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Description

The present invention relates to a series of new oligopeptides, which hav renin-inhibitory and, hence, hypotensive activities, and which are thus of particular value in the treatment of hypertension induced by failures in the renin-angiotensin system of the mammalian, especially human, body. The invention also relates to the preparation of such compounds and to their use in such treatment. The oligopeptides of the present invention include in their peptide chain a unit derived from the amino acid commonly known as cyclostatine, whose formal name is (3S, 4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid and which is also sometimes referred to as "ACHPA", or from an analogue thereof.

There is considerable evidence that reduction of elevated blood pressure reduces the risks of morbidity and mortality. Elevated blood pressure (hypertension) can be caused by a variety of factors and a large number of drugs is available for the treatment of hypertension, the drug of choice being dictated in large measure by the cause of the hypertension.

One of the factors known to play a role in the onset of hypertension in the mammalian body is an oligopeptide known as angiotensin II. Angiotensin I is a polypeptide formed by the action of renin upon a plasma protein, and this is converted to angiotensin II by the action of ACE (angiotensin converting enzyme). Angiotensin II causes constriction of the arterioles and can produce hypertension. Hypertension of this type can be reduced by reducing the plasma concentration of angiotensin I or II, which, in turn, can be achieved by inhibiting the activity of renin. The number of available drugs having this type of inhibitory activity is very limited, and, to date, no such drug is commercially available.

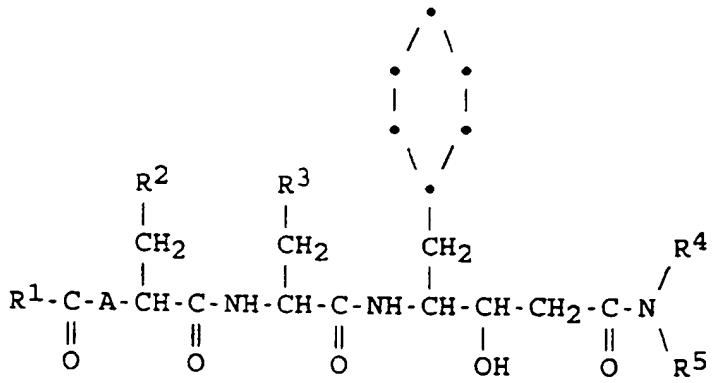
A variety of peptide derivatives having this type of activity is known. Those prior art compounds believed to be closest to the compounds of the present invention, in that they are based upon the rather uncommon amino acid statine and analogues thereof, are disclosed in EP-A 155 809, EP-A 184 855 and EP-A 186 977. Various other prior art discloses other polypeptides having renin-inhibitory activities, but which have some other amino acid unit in place of the cyclostatine unit, which is one of the critical features of the compounds of the present invention, for example US Patent No. 4 698 329 and EP-A 228 192.

We have now discovered a series of peptide derivatives having a very marked ability to inhibit the activity of renin, which ability is believed to be significantly better than that of the prior art compounds.

Certain of the compounds of the invention resemble certain of those disclosed in EP-A 155 809, although this European Patent Publication also discloses many other compounds which are not relevant to the present invention. However, the compounds of the present invention differ from those of EP-A 155 809 primarily in the nature of the groups at the nitrogen terminal end and at the carboxy terminal end of the oligopeptide chain. The compounds of the present invention differ from those of EP-A 184 855 primarily in the nature of the groups at the nitrogen terminal end of the oligopeptide chain. The compounds of the present invention differ from those of EP-A 186 977 primarily in the nature of the group at the nitrogen terminal end and also to some extent in the nature of the group at the carboxy terminal end of the oligopeptide chain. The compounds of the present invention differ from those of EP-A 228 192 in the nature of other units in the polypeptide chain.

The compounds of the present invention have, in general, a higher inhibitory activity against renin, much improved absorption when administered by the oral route, lower toxicity, better and stronger enzyme specificity and better water solubility than the compounds of the prior art. These advantages suggest that the compounds of the present invention will be of outstanding value in the treatment of disorders in the mammalian body arising from an imbalance in the level of renin in the blood. In particular, it is well known that the oral route is the preferred route of administration for drugs, particularly where (as with the drugs with which the present invention is concerned) drugs are intended for self-administration by the patient, generally over a long period of time. However, a serious disadvantage common to almost all of the known renin-inhibitory oligopeptides, including most of those mentioned in the previous paragraph, is that, in practice, it is necessary to administer them by parenteral routes, e.g. by injection, as suppositories or even by inhalation. This applies even in those cases where the compounds have been suggested for oral use, since it has subsequently been found that, except for those of EP-A 228 192, they either are insufficiently stable to enzymes, e.g. esterases, present in the digestive system or are inadequately absorbed from the stomach and/or intestines or both. Of cours , the poor stability is expected with oligop ptides, as the mammalian digestive system is sp cifically designed to break down compounds of that type. Consequently, ven if the compounds can be administered orally, such high doses ar nec ssary in order to mak up for poor absorption and/or losses caused by digestion as to mak oral administration impractical.

The compounds of the present invention are thus those compounds of formula (I):



(I)

wherein:

R^1 represents a 4-phenyl-1-piperazinyl, N-methyl-N-benzylamino, morpholino, N-methyl-N-cyclohexylaminomethyl, N-methyl-N-benzylaminomethyl, N-isopropyl-N-benzylaminomethyl, benzylaminomethyl, 4-phenyl-1-piperazinylmethyl, diethylaminomethyl, N-methyl-N-butylaminomethyl, N-methyl-N-phenylaminomethyl, morpholinomethyl, 3-morpholinopropyl, 4-(4-fluorophenyl)-1-piperazinylmethyl, 4-(4-chlorophenyl)-1-piperazinylmethyl, 4-(4-methoxyphenyl)-1-piperazinylmethyl, N-methyl-N-phenethylaminomethyl, diisobutylaminomethyl or 4-(4-chlorobenzhydryl)-1-piperazinylmethyl group;

R^2 represents a naphthyl group;

R^3 represents a thienyl, isoxazolyl, thiazolyl, imidazolyl or isopropyl group;

R^4 represents a 2-morpholinoethyl, propyl, butyl, isobutyl, pentyl, isopentyl, 2-methylbutyl, hexyl, 3-(2-oxo-1-pyrrolidinyl)propyl or 1-morpholinomethyl-2-methylbutyl group;

R^5 represents a hydrogen atom or a C_1 - C_8 alkyl group; and

A represents a group of formula -NH- or $-(CH_2)_n-$, in which n represents 1 or 2,

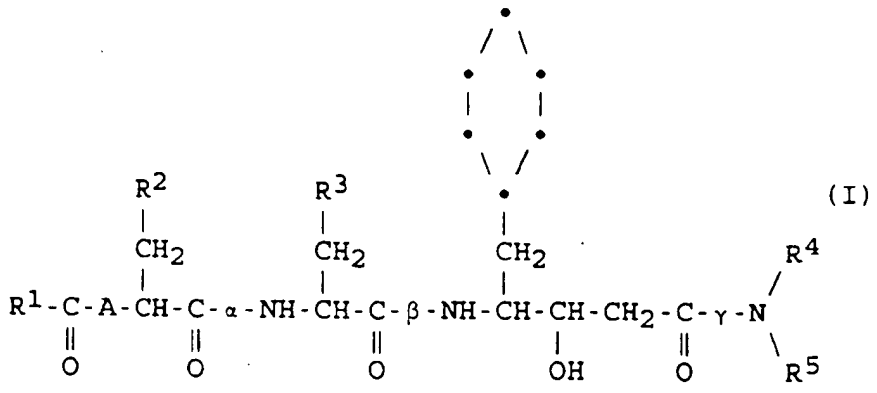
WITH THE PROVISO THAT when R^1 represents a benzylaminomethyl group, R^3 represents a thienyl, isoxazolyl or thiazolyl group,

and pharmaceutically acceptable salts thereof.

The invention also provides the use for the manufacture of a medicament for the treatment or prophylaxis of angiotensin-induced hypertension in a mammal, which may be human or non-human, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides a composition for the treatment of angiotensin-induced hypertension in a mammal, which may be human or non-human, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

The compounds of the invention may be prepared by reacting together two compounds, one having a t rminal carboxy group or reactive derivative thereof and the other having a terminal amino group or reactive derivative thereof, under conditions conventional for peptide synthesis, said two compounds corresponding to the fragments derivable by cleavage of any one of the peptide bonds marked α, β and γ in the following formula (I) and, where A is a group -NH-, between that group and the adjacent carboxy group:



(I)

(in which R^1 - R^5 and A are as defined above).

Where R^5 represents an alkyl group containing from 1 to 8 carbon atoms, this may be a straight or branched chain alkyl group and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, sec-pentyl, t-pentyl, hexyl, isohexyl, 2-methylbutyl, 1,2-dimethylbutyl, heptyl and octyl groups. R^5 more preferably represents a C_4 - C_6 alkyl group, e.g. a butyl, isobutyl, pentyl, isopentyl or hexyl group. However, R^5 most preferably represents a hydrogen atom.

The more preferred group which may be represented by R^2 is the 1-naphthyl group.

The more preferred groups which may be represented by R^3 include the 2-thienyl, 5-isoxazolyl, 4-thiazolyl 5-imidazolyl and isopropyl groups.

R^5 preferably represents a hydrogen atom or a propyl group, more preferably a hydrogen atom.

The compounds of the invention contain at least three asymmetric carbon atoms, that is to say the carbon atom to which the group represented by R^2CH_2 is attached, that to which the group represented by R^3CH_2 is attached and that to which the cyclohexylmethyl group is attached, and can, depending upon the values of the various substituent groups defined above, also contain other asymmetric carbon atoms. Accordingly, a variety of optical isomers are possible. The present invention envisages both the individual isolated isomers as well as mixtures (e.g. racemates) thereof. However, we particularly prefer those isomers in which: the carbon atom to which the group represented by R^2CH_2 is attached is in the S-configuration; the carbon atom to which the group represented by R^3CH_2 is attached is in the S-configuration; the carbon atom to which the cyclohexylmethyl group is attached is in the S-configuration. More preferred are those compounds in which the carbon atom to which the cyclohexylmethyl group is attached is in the S-configuration and the carbon atom to which the group represented by R^3CH_2 is attached is in the S-configuration, and still more preferred are those compounds in which all three of the carbon atoms referred to above are in the S-configuration. Where optically active starting materials are employed to produce the compounds of the invention and/or stereo-specific routes are employed, it may be possible to produce individual isomers of the compounds of the invention. In other cases, mixtures of various isomers may be produced and, in such a case, these mixtures may be used as such or the individual isomers may be isolated by well-known techniques.

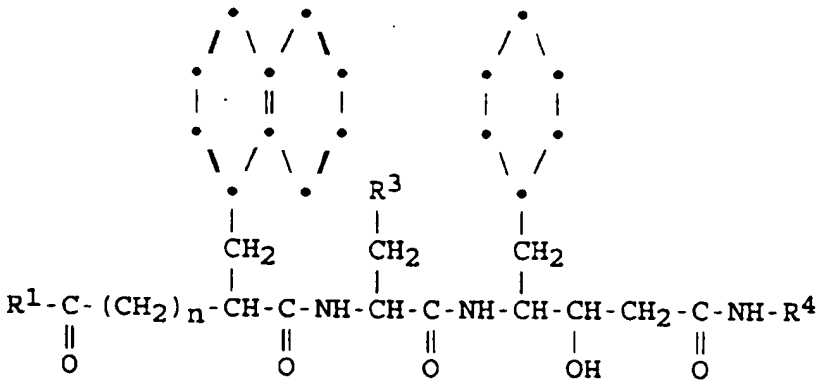
The compounds of the invention contain basic nitrogen atoms and, depending upon the value of certain of the substituents, may also contain free carboxy groups. Accordingly, the compounds of the invention will normally form acid addition salts and may, where they contain at least one carboxy group, also form salts with cations. The nature of the acid or cation employed to form such a salt is not critical to the invention, except where the compounds of the invention are intended for therapeutic use, in which case the resulting salt must be pharmaceutically acceptable which, as is well-known to those skilled in the art, means that the salt must not have an increased toxicity or substantially increased toxicity or a reduced activity or substantially reduced activity, as compared with the free compound of formula (I). However, where the compounds of the invention ar intended for non-therap utic use, e.g. as intermediates, ven this limitation need not apply.

Examples of acids which can b employed to form acid addition salts includ : mineral acids, such as hydrochloric acid, sulphuric acid and phosphoric acid; organic carboxylic acids, such as oxalic acid, mal ic acid, succinic acid and citric acid; and organic sulphonic acids, such as methan sulphonic acid, benzenesulphonic acid and p-toluenesulphonic acid. The compounds may also form salts with: alkali and alkaline earth metals, such as sodium, potassium, calcium and magn sium; and organic bases, such as

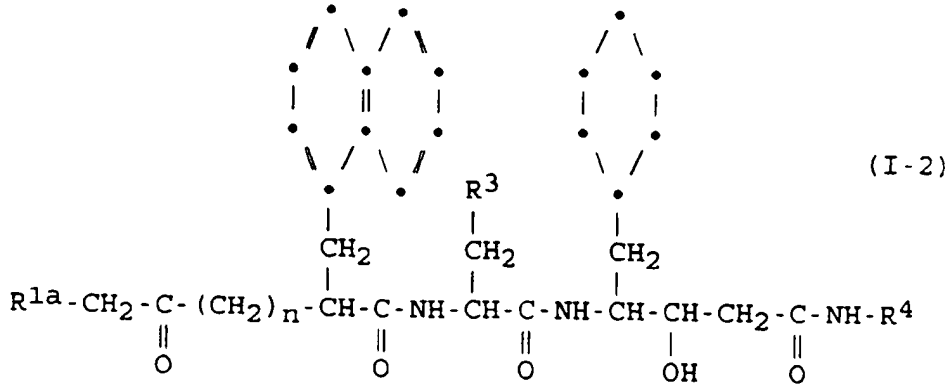
dicyclohexylamine.

Examples of specific compounds of the invention are given in the following formulae (I-1) to (I-8), in which the substituents are as defined in the corresponding one of Tables 1 to 6 [i.e. Table 1 relates to formula (I-1), Table 2 relates to formula (I-2) and so on]. The compounds of the invention are hereinafter, where appropriate, identified by the numbers appended to them in these Tables. In the Tables, the following abbreviations are used:

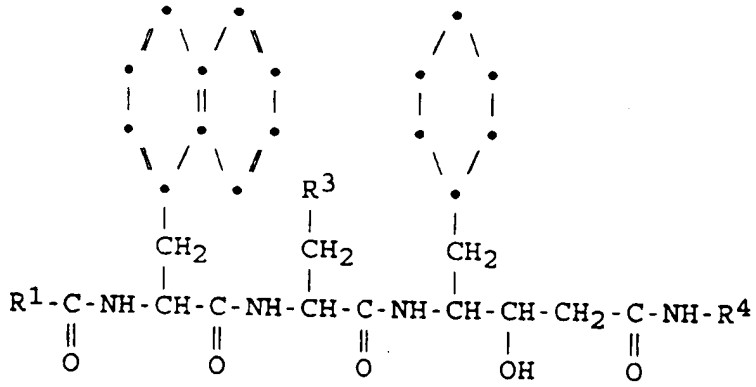
Bu	butyl
iBu	isobutyl
Bz	benzyl
Bzhy	benzhydryl
Et	ethyl
Hx	hexyl
cHx	cyclohexyl
Imid	imidazolyl
Isox	isoxazolyl
Me	methyl
Mor	morpholino
Np	naphthyl
Ph	phenyl
Piz	piperazinyl
Pn	pentyl
iPn	isopentyl
Pr	propyl
iPr	isopropyl
Pyrd	pyrrolidinyl
Thi	thienyl
Thiz	thiazolyl



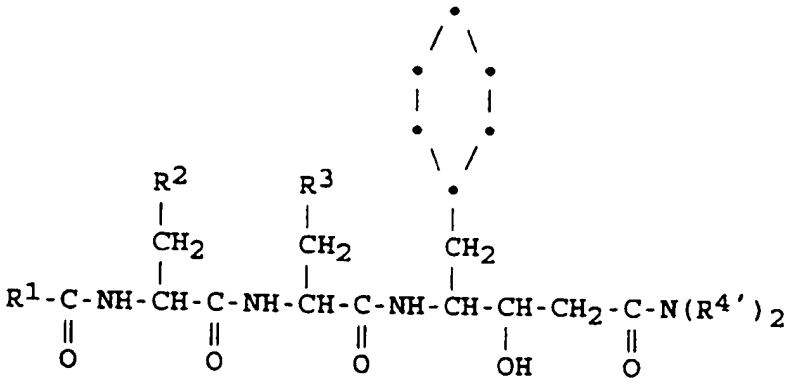
(I-1)



(I-2)



(I-4)



(I-7)

TABLE 1

Cpd No.	R^1	R^3	R^4	n
1-40	Mor	4-Thiz	2-MorEt	1
1-60	Mor	4-Isox	2-MorEt	1
1-66	Mor	5-Imid	2-MorEt	1
1-85	4-Ph-1-Piz	5-Imid	2-MorEt	1
1-86	4-Ph-1-Piz	4-Thiz	2-MorEt	1
1-88	4-Ph-1-Piz	5-Isox	2-MorEt	1
1-101	Bz(Me)N-	4-Thiz	2-MorEt	1
1-102	Mor	4-Thiz	3-(2-oxo-1-Pyrd)Pr	1
1-108	Bz(Me)N-	5-Isox	2-MorEt	1
1-109	Bz(Me)N-	5-Isox	3-(2-oxo-1-Pyrd)Pr	1
1-110	Mor	2-Thi	3-(2-oxo-1-Pyrd)Pr	1
1-111	Mor	2-Thi	2-MorEt	1
1-115	Mor	iPr	2-MorEt	1
1-117	Bz(Me)N-	iPr	2-MorEt	1
1-126	Mor	iPr	2-MeBu	1
1-131	Mor	4-Thiz	2-MeBu	1
1-132	Mor	4-Thiz	iPn	1
1-135	Bz(Me)N-	4-Thiz	2-MeBu	1
1-136	4-Ph-1-Piz	4-Thiz	2-MeBu	1
1-138	Mor	5-Isox	2-MeBu	1
1-140	Bz(Me)N-	5-Isox	2-MeBu	1
1-142	Mor	4-Thiz	2-MorEt	2
1-143	Mor	4-Thiz	3-(2-oxo-1-Pyrd)Pr	2
1-146	Bz(Me)N-	4-Thiz	2-MorEt	2

TABLE 2

Cpd No.	R^{1a}	R^3	R^4	n
2-1	Mor	4-Thiz	2-MorEt	1
2-3	Bz(Me)N-	4-Thiz	2-MorEt	1
2-4	4-Ph-1-Piz	4-Thiz	2-MorEt	1
2-5	Mor	4-Thiz	3-(2-oxo-1-Pyrd)Pr	1
2-6	Mor	5-Isox	3-(2-oxo-1-Pyrd)Pr	1
2-7	Mor	5-Isox	2-MorEt	1
2-8	Bz(Me)N-	iPr	2-MorEt	1
2-9	Mor	4-Thiz	2-MeBu	1
2-11	Bz(Me)N-	4-Thiz	2-MeBu	1

TABLE 4

Cpd. No.	R^1	R^3	R^4
4-15	$(Et_2N)Me$	4-Thiz	2-MorEt
4-16	[Bu(Me)N]Me	4-Thiz	2-MorEt
4-20	[Bu(Me)N]Me	5-Isox	2-MorEt
4-27	[Me(cHx)N]Me	4-Thiz	2-MorEt
4-28	[Me(Ph)N]Me	4-Thiz	2-MorEt
4-30	[Me(Bz)N]Me	4-Thiz	2-MorEt
4-32	[Me(2-PhEt)N]Me	4-Thiz	2-MorEt
4-45	MorMe	5-Imid	2-MorEt
4-55	MorMe	4-Thiz	2-MorEt
4-74	MorMe	5-Isox	2-MorEt

TABLE 4 (cont)

Cpd. No.	R^1	R^3	R^4
4-79	MorMe	2-Thi	2-MorEt
4-101	3-MorPr	4-Thiz	2-MorEt
4-104	3-MorPr	5-Isox	2-MorEt
4-110	(4-Ph-1-Piz)Me	4-Thiz	2-MorEt
4-112	(4-Ph-1-Piz)Me	5-Isox	2-MorEt
4-114	[4-(4-FPh)- -1-Piz]Me	5-Isox	2-MorEt
4-115	[4-(4-FPh)- -1-Piz]Me	4-Thiz	2-MorEt
4-116	[4-(4-MeOPh)- -1-Piz]Me	4-Thiz	2-MorEt
4-130	(BzNH)Me	4-Thiz	2-MorEt
4-131	Me(cHx)NMe	5-Isox	2-MorEt
4-166	Me(cHx)NMe	2-Thi	2-MorEt
4-167	Me(Bz)NMe	2-Thi	2-MorEt
4-171	(4-Ph-1-Piz)Me	2-Thi	2-MorEt
4-172	[4-(4-FPh)- -1-Piz]Me	2-Thi	2-MorEt
4-179	MorMe	4-Thiz	3-(2-oxo-1-Pyrd)Pr
4-191	MorMe	iPr	3-(2-oxo-1-Pyrd)Pr
4-192	MorMe	iPr	2-MorEt
4-193	Me(cHx)NMe	iPr	2-MorEt
4-194	Me(cHx)NMe	iPr	3-(2-oxo-1-Pyrd)Pr
4-195	Me(Ph)NMe	iPr	3-(2-oxo-1-Pyrd)Pr
4-196	Me(Ph)NMe	iPr	2-MorEt
4-197	Me(Bz)NMe	iPr	2-MorEt
4-198	Me(Bz)NMe	iPr	3-(2-oxo-1-Pyrd)Pr
4-199	Me(Bu)NMe	iPr	3-(2-oxo-1-Pyrd)Pr
4-200	Me(Bu)NMe	iPr	2-MorEt
4-201	[Me(2-PhEt)N]Me	iPr	2-MorEt

TABLE 4 (cont)

Cpd. No.	R^1	R^3	R^4
4-204	[4-(4-FPh)--1-Piz]Me	iPr	2-MorEt
4-207	Me(Bz)NMe	5-Imid	2-MorEt
4-208	Me(Bz)NMe	5-Imid	3-(2-oxo-1-Pyrd)Pr
4-209	Me(cHx)NMe	5-Imid	3-(2-oxo-1-Pyrd)Pr
4-210	Me(cHx)NMe	5-Imid	2-MorEt
4-211	(4-Ph-1-Piz)Me	5-Imid	2-MorEt
4-212	(4-Ph-1-Piz)Me	5-Imid	3-(2-oxo-1-Pyrd)Pr
4-214	iBu_2NMe	4-Thiz	2-MorEt
4-216	iPr(Bz)NMe	5-Isox	2-MorEt
4-217	Me(Bz)NMe	5-Isox	2-MorEt
4-218	[4-(4-ClBzhy)--1-Piz]Me	4-Thiz	2-MorEt
4-219	iPr(Bz)NMe	4-Thiz	2-MorEt
4-220	[4-(4-ClPh)--1-Piz]Me	4-Thiz	2-MorEt
4-237	Me(cHx)NMe	5-Isox	3-(2-oxo-1-Pyrd)Pr
4-238	Me(Bz)NMe	5-Isox	3-(2-oxo-1-Pyrd)Pr
4-240	(4-Ph-1-Piz)Me	5-Isox	3-(2-oxo-1-Pyrd)Pr
4-241	MorMe	5-Isox	2-MeBu
4-242	(4-Ph-1-Piz)Me	5-Isox	2-MeBu
4-243	Me(cHx)NMe	5-Isox	2-MeBu
4-244	Me(Bz)NMe	5-Isox	2-MeBu
4-245	Me(Bz)NMe	4-Thiz	2-MeBu
4-246	Me(cHx)NMe	4-Thiz	2-MeBu
4-247	(4-Ph-1-Piz)Me	4-Thiz	2-MeBu
4-248	MorMe	4-Thiz	2-MeBu
4-250	MorMe	4-Thiz	iBu
4-253	MorMe	iPr	2-MeBu
4-254	MorMe	5-Imid	2-MeBu

TABLE 4 (cont)

Cpd. No.	R^1	R^3	R^4
4-255	Me(cHx)NMe	5-Imid	2-MeBu
4-258	MorMe	4-Thiz	Pr
4-260	MorMe	4-Thiz	Bu
4-262	MorMe	4-Thiz	Pn
4-263	MorMe	4-Thiz	iPn
4-265	MorMe	4-Thiz	Hx
4-272	MorMe	5-Isox	Pr
4-273	MorMe	5-Isox	iBu
4-274	MorMe	5-Isox	Pn
4-276	MorMe	5-Imid	Pr
4-277	MorMe	5-Imid	iBu
4-278	MorMe	5-Imid	Pn
4-279	MorMe	5-Imid	iPn
4-280	MorMe	5-Imid	Hx
4-282	MorMe	2-Thi	Hx
4-290	Me(Bz)NMe	4-Thiz	Pr
4-291	Me(Bz)NMe	4-Thiz	iBu
4-292	Me(Bz)NMe	4-Thiz	iPn
4-294	Me(Ph)NMe	4-Thiz	iPn
4-295	Me(Ph)NMe	2-Thi	Pn
4-297	Me(cHx)NMe	4-Thiz	Bu
4-298	Me(cHx)NMe	4-Thiz	Hx
4-299	Me(cHx)NMe	5-Imid	Pn
4-300	Me(Bz)NMe	5-Imid	2-MeBu
4-301	Me(Bz)NMe	5-Imid	Hx
4-303	Me(Bz)NMe	iPr	Hx
4-304	Me(Bz)NMe	iPr	2-MeBu

TABLE 7

Cpd. No.	R^1	R^2	R^3	$R^{4'}$
7-1	MorMe	1-Np	4-Thiz	iBu
7-2	MorMe	1-Np	4-Thiz	Pn
7-4	MorMe	1-Np	5-Isox	Bu

Also preferred are the pharmaceutically acceptable salts of the above compounds, especially the hydrochlorides.

Of the compounds listed above, the following compounds are preferred, that is to say Compounds No. 1-40, 1-86, 1-101, 1-108, 1-131, 1-146, 4-15, 4-16, 4-27, 4-28, 4-30, 4-45, 4-55, 4-79, 4-101, 4-115, 4-116, 4-131, 4-179, 4-191, 4-192, 4-193, 4-194, 4-195, 4-196, 4-197, 4-198, 4-199, 4-201, 4-208, 4-214, 4-217, 4-218, 4-219, 4-237, 4-238, 4-241, 4-244, 4-248, 4-250, 4-258, 4-260, 4-262, 4-263, 4-265, 4-298, 4-300 and 4-304, of which the following are most preferred:

1-40. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide and N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

1-101. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

1-108. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

1-131. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide, especially N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide;

4-27. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

4-28. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[N-(N-methylanilinoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

4-194. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide, especially N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide;

4-208. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-imidazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide;

4-217. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

4-218. N-[N-{N-[4-(4-Chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-alanyl}-3-(4-thiazolyl)-alanyl]-cyclostatin-(2-morpholinoethyl)amide, especially N-[N-{N-[4-(4-chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide;

4-219. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide, especially N-{N-[N-(N-benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide;

4-237. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide;

4-238. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide;

4-241. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amide;

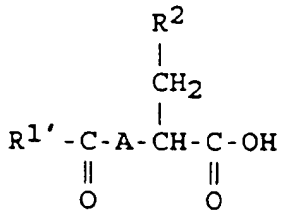
4-248. N-{N-[N-Morpholinoac tyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amide, especially N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide;

4-250. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-isobutylamide;

4-258. N-{N-[N-Morpholinoac tyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-propylamide;

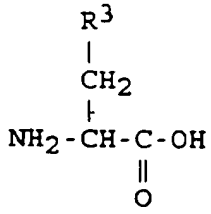
4-260. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-butylamide;
4-262. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-pentylamide;
4-263. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-isopentylamide;
4-265. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-hexylamide, especially N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamide; and the pharmaceutically acceptable salts of the above compounds, especially the hydrochlorides.

The compounds of the present invention are oligopeptides and may, therefore, be prepared, as is well known in the art by reacting together the component amino acids in any appropriate order, by reacting together two or more lower oligopeptides (again, if necessary, in an appropriate order) or by reacting one or more component amino acids with one or more lower oligopeptides (again, if necessary, in an appropriate order). However, provided that the correct sequence of amino acid residues in the oligopeptide of formula (I) is achieved, there is no particular restriction upon the order in which these reactions are carried out. In general terms, the compounds of the invention may be prepared by reacting together compounds of formulae:



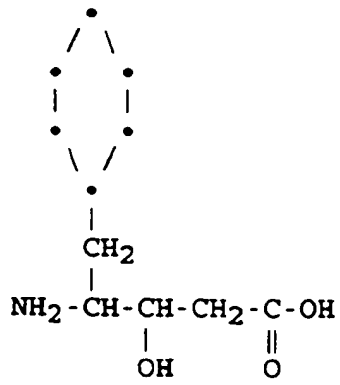
(IV)

or a reactive derivative thereof,



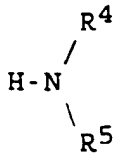
(V)

or a reactive derivative thereof,



(VI)

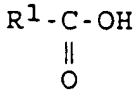
or a reactive derivative thereof, and



(VII)

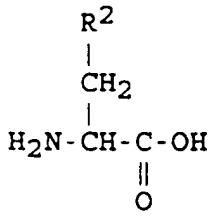
or a reactive derivative thereof (in the above formulae R^2 - R^5 and A are as defined above and $R^{1'}$ represents any of the groups represented by R^1 or an active group), and, where $R^{1'}$ represents said active group, converting it to any one of the groups represented by R^1;

or by reacting a peptide compound derivable by reaction of some of said compounds of formulae (IV), (V), (VI) or (VII) or said reactive derivatives with the remainder of said compounds or said reactive derivative(s) or with a peptide compound or compounds derivable by reaction of said remainder or reactive derivative(s) thereof, the reaction(s) being in an order corresponding to the order of the residues derived from said compounds of formulae (IV), (V), (VI) and (VII) in said compound of formula (I). Also, where A represents a group of formula -NH-, the compound of formula (IV) may, if desired, be replaced by the two compounds of formulae (IVa) and (IVb):



(IVa)

and



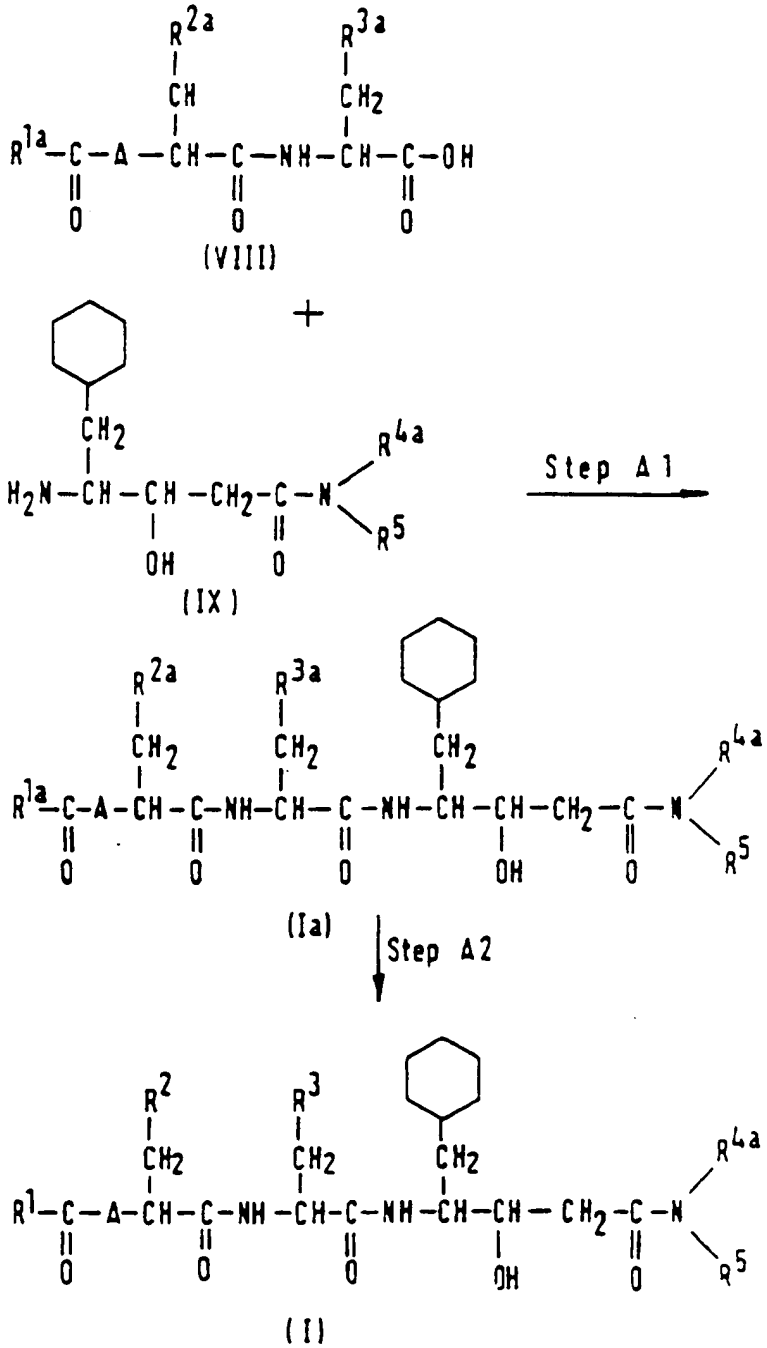
(IVb)

(in which R^1 and R^2 are as defined above).

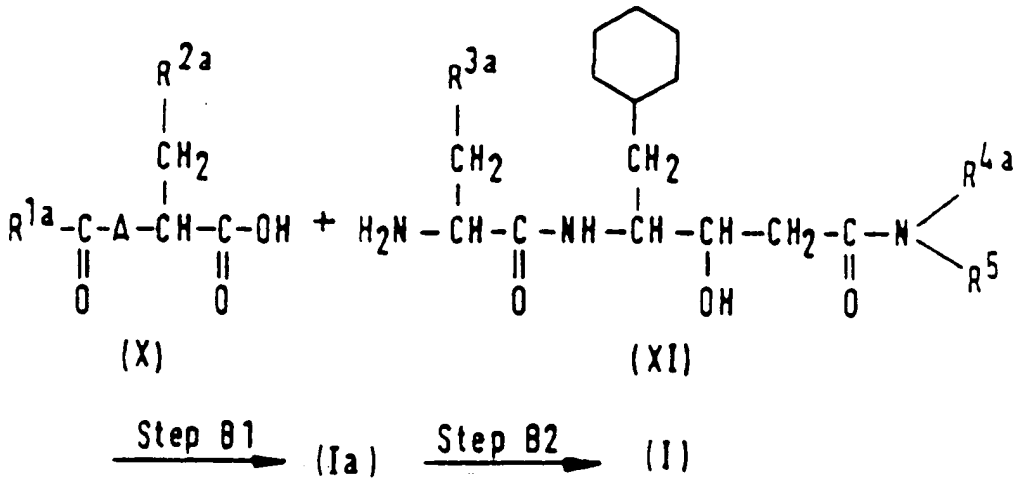
If required, the resulting compound of formula (I) may be subjected to any one or more of various optional reactions, for example salification.

In specific embodiments of the process of the present invention, the compounds of the invention may be prepared by any of the following Reaction Schemes A, B, C, D and E.

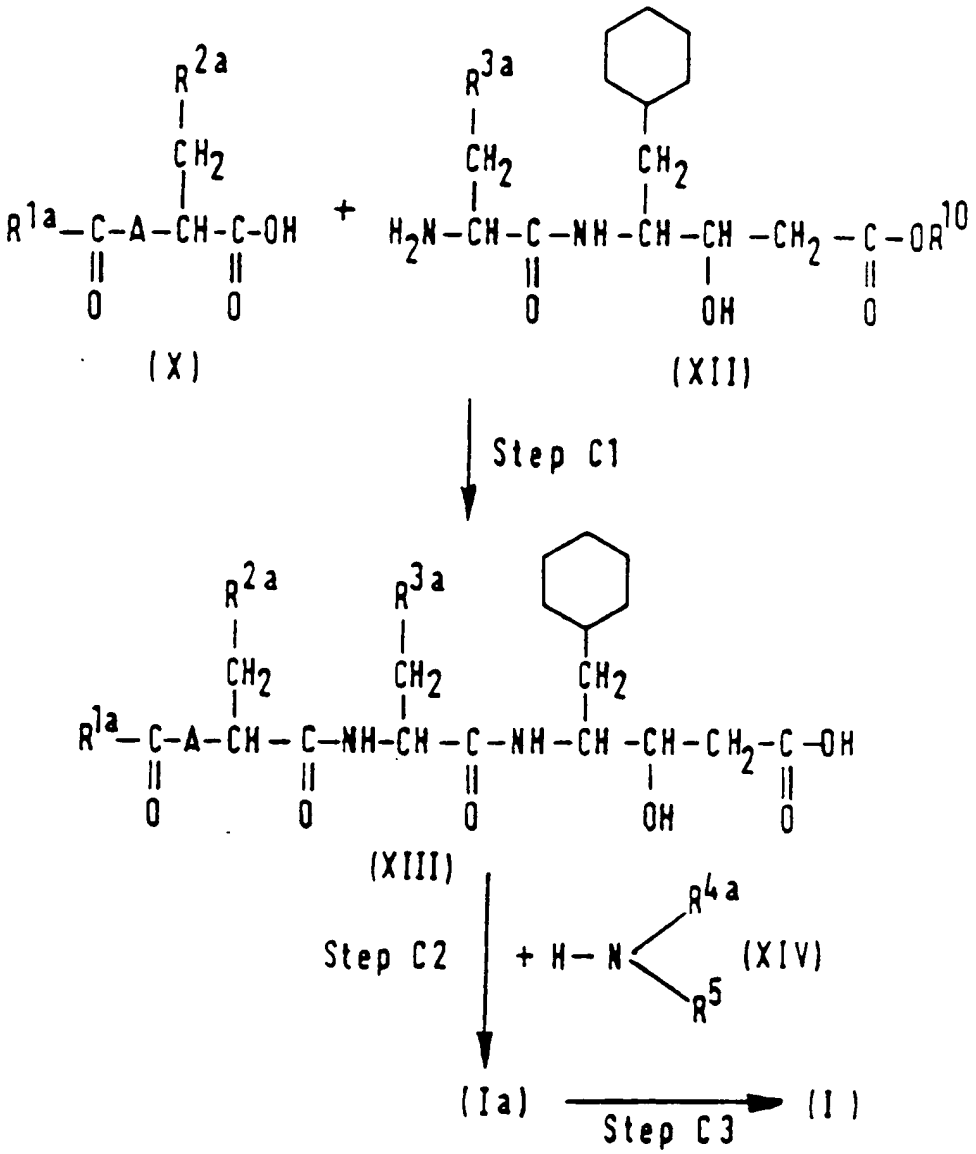
Reaction Scheme A



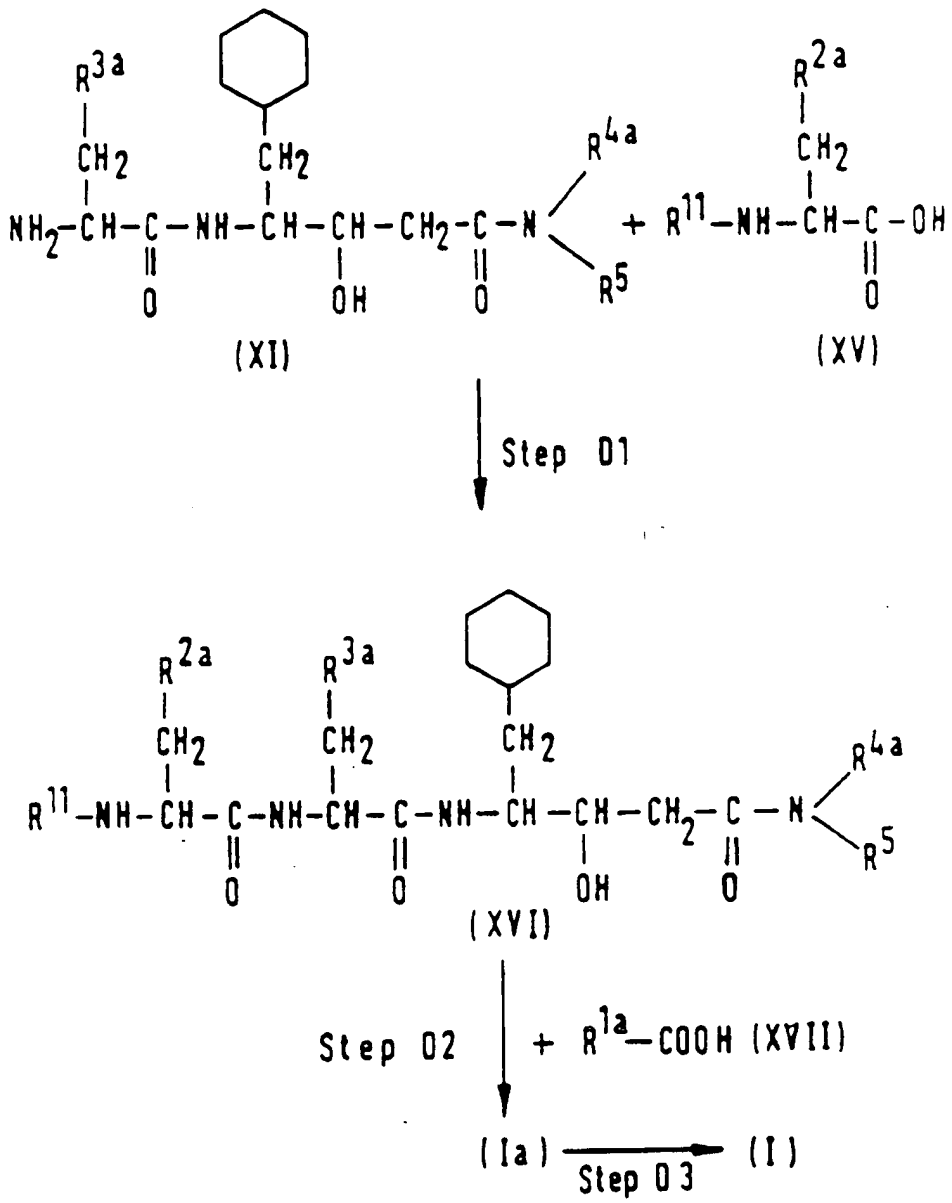
Reaction Scheme 8



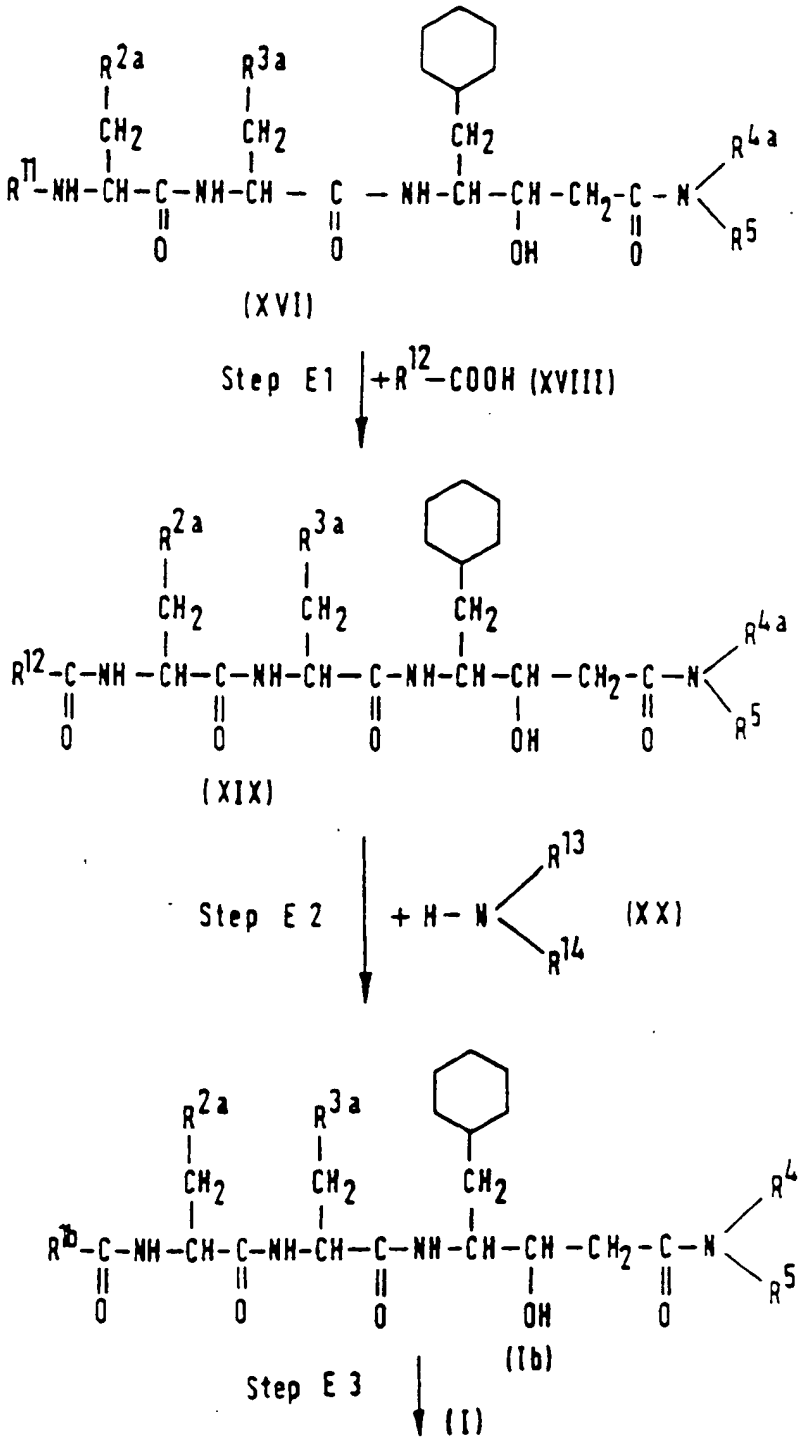
Reaction Scheme C



Reaction Scheme 0



Reaction Scheme E



In the abov formula , R^1, R^2, R^3, R^4, R^5 and A are as defined above; R^{1a}, R^{2a}, R^{3a} and R^{4a} may r present any of th groups d fined for R^1, R^2, R^3 and R^4, respectiv ly, but in which any groups which may undesirably participate in the respective r actions have been protected; R^{1b} repres nts an N-methyl-N-cyclohexylaminomethyl, N-m thyl-N-benzylaminomethyl, N-isopropyl-N-benzylaminom thyl, benzylaminomethyl, 4-phenyl-1-piperazinylmethyl, di thylaminomethyl, N-methyl-N-butylaminomethyl, N-methyl-N-ph nylamin methyl, morpholinomethyl, 3-morpholinopropyl, 4-(4-fluorophenyl)-1-piperazinylmethyl, 4-

(4-chlorophenyl)-1-piperazinylmethyl, 4-(4-methoxyphenyl)-1-piperazinylmethyl, N-methyl-N-phenethylaminomethyl, diisobutylaminomethyl or 4-(4-chlorobenzhydryl)-1-piperazinylmethyl group;

In these reactions, the free acids and amides shown may, if desired or if required by the particular reaction chosen, be replaced by an appropriate active derivative, as described in more detail hereafter.

There is no particular restriction on the nature of the protecting group which may be represented by R^{1a}, R^{4a} and R^{11}, and any such group commonly used in the field of amino acid chemistry may equally be employed here. For example, suitable amino-protecting groups include: carbonate residues, especially aralkyloxycarbonyl groups, such as the benzyloxycarbonyl and p-methoxybenzyloxycarbonyl groups, alkoxycarbonyl groups, such as the t-butoxycarbonyl group, and other carbonate residues, such as the 9-fluorenylmethyloxycarbonyl groups. Examples of imino-protecting groups include the 2,4-dinitrophenyl group.

The principal reactions in Reaction Schemes A, B, C, D and E are standard condensation reactions of the type conventionally used in peptide synthesis and they may be carried out according to any of the well known techniques employed in peptide synthesis, for example by the azide method, the active ester method, the mixed acid anhydride method, the carbodiimide method or the condensation method. The reactive derivatives employed in these reactions are those reactive derivatives conventionally employed in such methods. Certain of these methods are described in more detail below.

Azide Method

First, the carboxylic acid of formula (VIII) (Reaction Scheme A), (X) (Reaction Scheme B or C), (XIII) (Reaction Scheme C), (XV) (Reaction Scheme D), (XVII) (Reaction Scheme D) or (XVIII) (Reaction Scheme E), as such, or, more usually, in the form of its corresponding alkyl ester, is treated with hydrazine in an inert solvent, to give the corresponding acid hydrazide. The nature of the solvent employed is not critical and any solvent commonly employed in this type of reaction may equally be employed here; however, we generally find it convenient to use a polar solvent, especially a fatty acid amide, such as dimethylformamide. Also, the reaction temperature is not critical and the reaction will take place over a wide range of temperatures; we generally find it convenient to carry out the reaction at about ambient temperature. The resulting hydrazide is then reacted with a nitrite, to convert it into an azide, after which the azide is reacted with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E).

Examples of nitrites which may be employed include: alkali metal nitrites, such as sodium nitrite; and alkyl nitrites, such as isoamyl nitrite.

The reaction of the acid hydrazide with the nitrite and the subsequent reaction of the resulting azide with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E) are commonly carried out in the same reaction solution, without intermediate isolation of the azide. Both reactions are preferably carried out in the presence of an inert solvent. The nature of the solvent is not critical, provided that it does not interfere with the reaction. Suitable solvents include, for example: amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and pyrrolidones, such as N-methylpyrrolidone. Although there is no criticality as to the reaction temperature, the reaction with the nitrite is preferably effected at a relatively low temperature, e.g. from -50°C to 0°C, whilst the reaction of the azide with the amine is preferably effected at a temperature of from -10°C to +10°C. The time required for each of these reactions will vary, depending upon the nature of the reagents and the reaction temperature, but a period of from 5 minutes to 1 hour and a period of from 10 hours to 5 days will normally suffice for the reaction with the nitrite and the reaction of the azide with the amine, respectively.

Active Ester Method

In this method, the carboxylic acid of formula (VIII) (Reaction Scheme A), (X) (Reaction Scheme B or C), (XIII) (Reaction Scheme C), (XV) (Reaction Scheme D), (XVII) (Reaction Scheme D) or (XVIII) (Reaction Scheme E) is first converted to an active ester by reacting it with a suitable reagent for producing active esters, after which this active ester is reacted with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E).

Formation of the active ester is preferably effected by reacting the carboxylic acid of formula (VIII), (X), (XIII), (XV), (XVII) or (XVIII) with, for example, an N-hydroxyimide compound, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole or N-hydroxy-5-norbornene-2,3-dicarboximide. The reaction to form the

active ester is preferably effected in the presence of a condensing agent, such as dicyclohexylcarbodiimide or carbonyldiimidazole.

The reaction to form the active ester is preferably effected in the presence of an inert solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: halogenated hydrocarbons, preferably halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; ethers, such as diethyl ether or tetrahydrofuran; and amides, such as dimethylformamide or dimethylacetamide.

The reaction temperature may vary over a wide range, for example from -10°C to room temperature. The time required for the reaction may also vary widely, depending upon the nature of the reagents and upon the reaction temperature, but a period of from 30 minutes to 10 hours will normally suffice.

Reaction of this active ester with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E) may be carried out with or without intermediate isolation of the active ester. Reaction of the active ester with the amine is preferably effected in the presence of an inert solvent, examples of which are as given for the preparation of the active ester itself. The temperature required for the reaction is not particularly critical and, for this reason, we normally prefer to carry out the reaction at about ambient temperature. The time required for the reaction will vary widely, but a period of from 30 minutes to 10 hours will normally suffice.

Mixed Acid Anhydride Method

In this method, the carboxylic acid of formula (VIII) (Reaction Scheme A), (X) (Reaction Scheme B or C), (XIII) (Reaction Scheme C), (XV) (Reaction Scheme D), (XVII) (Reaction Scheme D) or (XVIII) (Reaction Scheme E) is first converted to a mixed acid anhydride, and this is then reacted with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E).

Preparation of the mixed acid anhydride is effected by reacting the acid of formula (VIII), (X), (XIII), (XV), (XVII) or (XVIII) with a suitable reagent, preferably in the presence of an inert solvent. Suitable reagents include: lower alkyl haloformates, such as ethyl chloroformate or isobutyl chloroformate; and di-(lower alkyl) cyanophosphonates, such as diethyl cyanophosphonate. Examples of suitable inert solvents include the amides and ethers referred to in relation to the active ester method.

This reaction is preferably effected in the presence of an organic amine, such as triethylamine or N-methylmorpholine. The reaction temperature may vary over a wide range, for example from -10°C to room temperature. The period required for the reaction will also vary widely, depending upon such factors as the nature of the reagents and the reaction temperature, but a period of from 30 minutes to 5 hours will normally suffice.

Reaction of the resulting mixed acid anhydride with the amine of formula (IX), (XI), (XII), (XIV) or (XVI) is preferably effected in the presence of an inert solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include the amides and ethers hereinbefore exemplified in relation to the active ester method. The reaction will take place over a wide range of temperatures, but we generally find it convenient to carry out the reaction at a temperature of from 0°C to about ambient temperature. The time required for the reaction will vary, depending upon many factors, such as the nature of the reagents and the reaction temperature, but a period of from 1 hour to 24 hours will normally suffice.

Condensation Method

In this method, the carboxylic acid of formula (VIII) (Reaction Scheme A), (X) (Reaction Scheme B or C), (XIII) (Reaction Scheme C), (XV) (Reaction Scheme D), (XVII) (Reaction Scheme D) or (XVIII) (Reaction Scheme E) is directly reacted with the amine of formula (IX) (Reaction Scheme A), (XI) (Reaction Scheme B or D), (XII) (Reaction Scheme C), (XIV) (Reaction Scheme C) or (XVI) (Reaction Scheme D or E). Such a reaction is preferably effected in the presence of a condensing agent, such as dicyclohexylcarbodiimide or carbonyldiimidazole. Otherwise, the reaction conditions and solvents are similar to those already described in relation to the active ester method.

The above reactions are the reactions involved in Steps A1, B1, C1, C2, D1, D2 and E1 of Reaction Schemes A, B, C, D and E. The other reactions involved are as follows.

Step C1

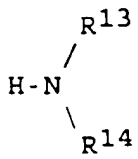
In Reaction Scheme C, Step C1, the reaction involves the reaction of an acid of formula (X) with an amine of formula (XII), as described generally above, followed by hydrolysis to remove the group represented by R^{10}. The hydrolysis reaction may be carried out as described in relation to the removal of carboxy protecting groups hereafter.

Step D2

In Reaction Scheme D, Step D2, the amino-protecting group R^{11} is first removed, before subjecting the resulting compound to reaction with an acid of formula (XVII), as described generally above. Removal of the amino-protecting group may take place as described hereafter in relation to the removal of protecting groups generally.

Step E2

In this step, the compound of formula (XIX), prepared as in Step E1, is reacted with a compound of formula (XX):



(XX)

(in which R^{13} and R^{14} are as defined above), to give a compound of formula (Ib). The reaction is preferably carried out by treating the compound (XIX) with the amine of formula (XX) in an inert solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction. Suitable solvents are as described above in relation to the peptide-forming reaction of acids and amines in the active ester reaction.

The reaction is preferably carried out in the presence of a base, the nature of which is not critical to the reaction. Suitable bases include, for example: alkali metal carbonates and bicarbonates, such as sodium carbonate, potassium carbonate or sodium bicarbonate; and organic amines, such as triethylamine or N-methylmorpholine.

The reaction will take place over a wide range of temperatures, and the precise temperature chosen is not critical to the invention. However, we generally find it convenient to carry out the reaction at a temperature in the range from -30°C to +100°C (more preferably from 0°C to 50°C). The time required for this reaction will vary, depending upon the nature of the reagents and the reaction temperature, but a period of from 30 minutes to 2 days will normally suffice.

Protecting Reactive Groups

Where the reagents employed in any of the above reactions, that is to say the carboxylic acids of formulae (VIII), (X), (XV), (XVII) and (XVIII) or the amines of formulae (IX), (XI), (XII), (XIV), (XVI) and (XX) or their reactive derivatives, contain active groups (e.g. amino, carboxy or imino groups including e.g. the imino group in the imidazolyl moiety of histidine) which are not intended to take part in peptide bond formation but which might interfere with the above reactions or undesirably participate in them, it is desirable that these groups should be protected before the reaction to form the peptide linkage and then, after that reaction, that the protected groups should be deprotected.

There is no particular limitation on the nature of the protecting group employed and such groups are well-known in peptide chemistry. For example, suitabl amino-protecting groups include: carbonat residues, such as the benzyloxycarbonyl, p-m thoxybenzyloxycarbonyl, t-butoxycarbonyl and 9-fluorenylmethyloxycarbonyl groups. Suitable carboxy-protecting groups include the low r alkyl groups, .g. the m thyl, ethyl, propyl or t-butyl groups, and aralkyl groups, such as th benzyl group. Examples of imino-protecting groups include the 2,4-dinitrophenyl group.

The protecting groups may be inserted and then r moved by conventional methods. For xample, wher the amino-prot cting group is a t-butoxycarbonyl group or th carboxy-protecting group is a t-butyl

group, this group may be removed by treatment with an acid (e.g. hydrochloric acid, hydrofluoric acid, trifluoroacetic acid or boron trifluoride, preferably in the form of a complex, e.g. the diethyl etherate), optionally in the presence of a cation scaveng r (e.g. anisol or thioanisole). Such a reaction is pr ferably effected in an inert solvent. The nature of the solvent is not critical, provided that it has no adverse effect on the reaction, and examples of suitable solvents include: ethers, such as dioxane; lower alcohols, such as methanol; and amides, such as dimethylformamide. The reaction will take place over a wide range of temperatures, and the precise temperature chosen is not critical; we generally find it convenient to carry out the reaction at, for example, a temperature of from 0°C to 30°C. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, a period of from 20 minutes to 1 hour will normally suffice.

When the amino or imino group is protected by an aralkyloxycarbonyl group or other carbonate residue and when the carboxy group is protected by an aralkyl group, the protecting group can be removed by catalytic reduction of the protected compound in the presence of hydrogen (for example under a hydrogen pressure of from atmospheric to 10 atmospheres) and in the presence of a suitable hydrogenation catalyst, for example palladium-on-carbon or palladium black. The reaction is preferably effected in the presence of an inert solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction, and examples of suitable solvents include: lower alcohols, such as methanol or ethanol; and ethers, such as tetrahydrofuran. We generally find it convenient to carry out the reaction at about ambient temperature, although this is not critical. The time required for the reaction may vary widely, but a period of from 30 minutes to 8 hours will normally suffice.

When the carboxy group is protected by a lower alkyl group, the protecting group may be removed by reacting the protected compound with an alkali (e.g. an alkali metal compound, preferably hydroxide, such as sodium hydroxide or potassium hydroxide). The reaction is preferably effected in a solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction. An aqueous solvent, such as aqueous methanol or aqueous ethanol is normally preferred. The reaction will take place over a wide range of temperatures, e.g. from 0 to 30°C. The time required for the reaction may vary widely, but a period of from 30 minutes to 5 hours will normally suffice.

Where the imino nitrogen atom in the imidazole moiety of a histidine residue is protected by a 2,4-dinitrophenyl, this may be removed by treating the protected compound with 2-mercaptoethanol. The reaction temperature is not critical, and we generally find it convenient to carry out the reaction at about ambient temperature.

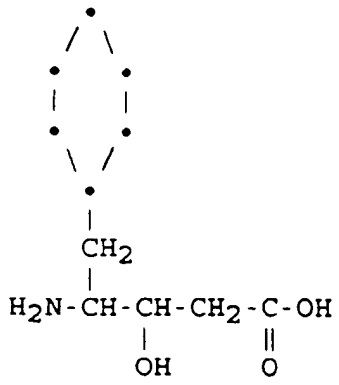
Conversion Reactions

If desired, certain groups in the compound of formula (I) prepared as described above may be converted to certain other groups by appropriate reactions well-known in the field of peptide synthesis. For xample, if desired, any acyl group within the resulting compound of formula (I) may be converted to any other acyl group; the reactions and reaction conditions involved in such conversions are well known in the art.

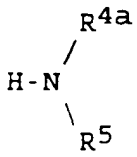
After completion of any of the above reactions or of the final such reaction, the desired compound may be isolated from the reaction mixture by conventional means. For example, one suitable recovery procedure comprises: if necessary, neutralizing the reaction mixture; removing the insoluble residue, if any, by filtration; and then distilling off the solvent to give the desired compound. If necessary, this compound may b further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, such as column chromatography or preparative thin layer chromatography.

Preparation of Starting Materials

The starting material of formula (IX) (Reaction Scheme A) may be prepared, for example, by protecting the amino group of cyclostatine or an analogue thereof, which is a compound of formula:



by conventional means, reacting the resulting protected compound with an amine of formula:



(XXa)

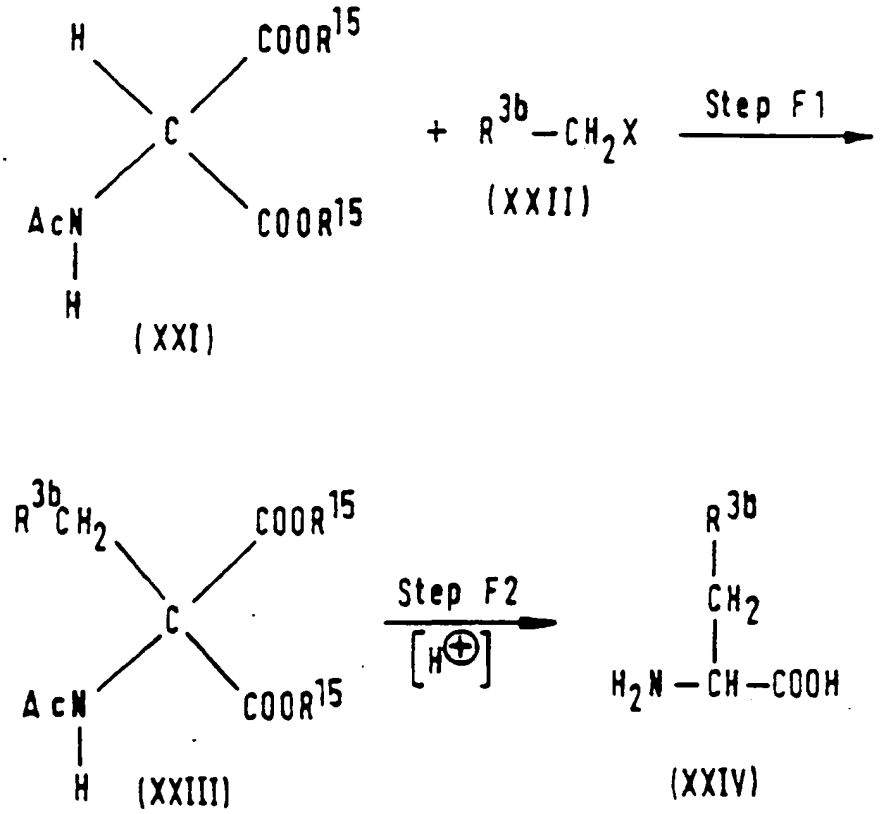
by a procedure similar to that described above in relation to Step C2 or E2, and then removing the protecting group. The cyclostatine or analogue thereof may be prepared by the method of J. Boger et al. [J. Med. Chem., 28, 1779 (1985)].

Also, in Reaction Scheme C, certain of the starting materials of formula (XII) are known compounds, or they may be prepared, for example, as described by R. P. Ahlqist [Prog. Drug Res., 20, E. Junker, Ed., Birkhauser Verlag (1976)].

Certain of the other starting materials employed in Reaction Schemes A - E, described above, may be prepared as illustrated in the following Reaction Schemes F - J.

Thus, alanine derivatives having an aromatic heterocyclic group as a substituent at the 3-position can easily be prepared by the reactions shown in Reaction Scheme F:

Reaction Scheme F

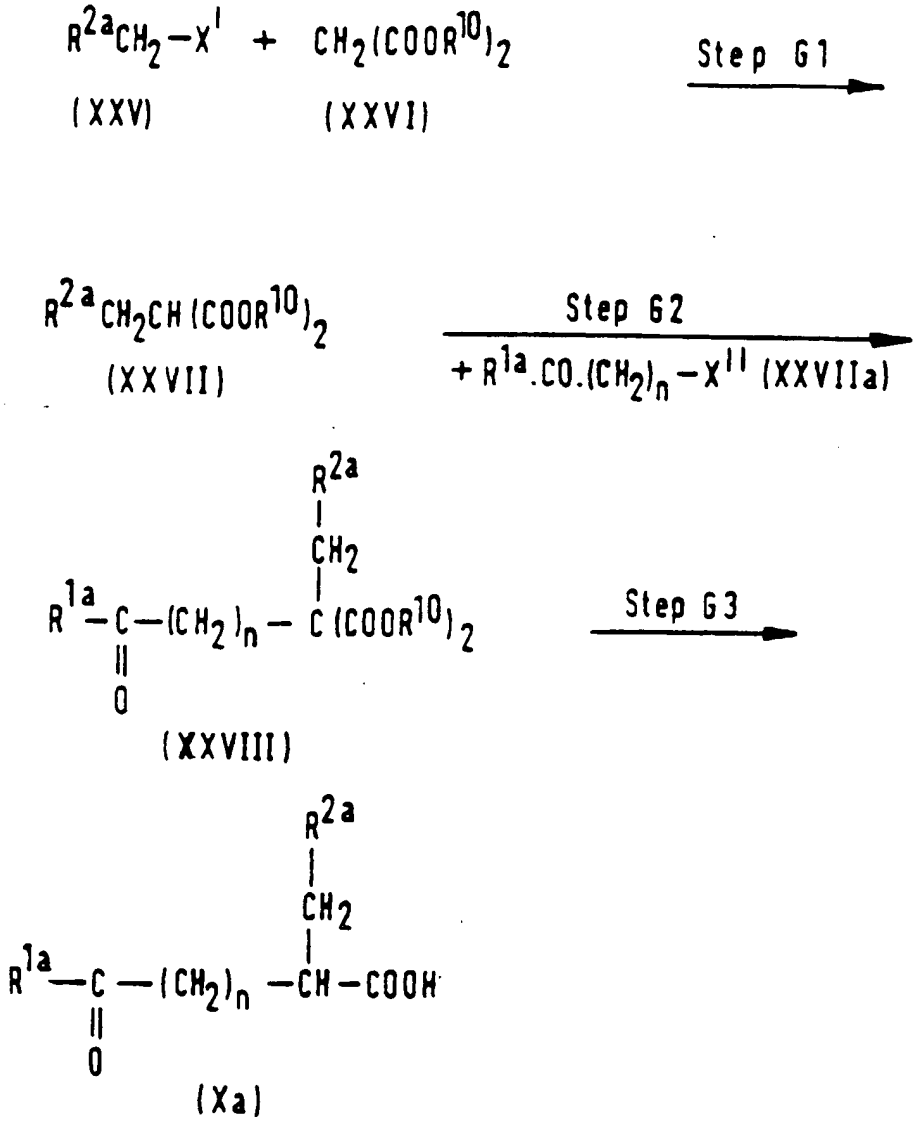


In the above formulae, Ac represents an acetyl group (although this can, if desired, be replaced by another amino-protecting group, e.g. as illustrated above); R^{3b} represents an aromatic heterocyclic group (as included in the groups defined above for R^3); X represents a halogen atom (preferably a bromine atom); and R^{15} represents a lower alkyl group or other carboxy-protecting group removable by treatment with an acid (preferably an ethyl group).

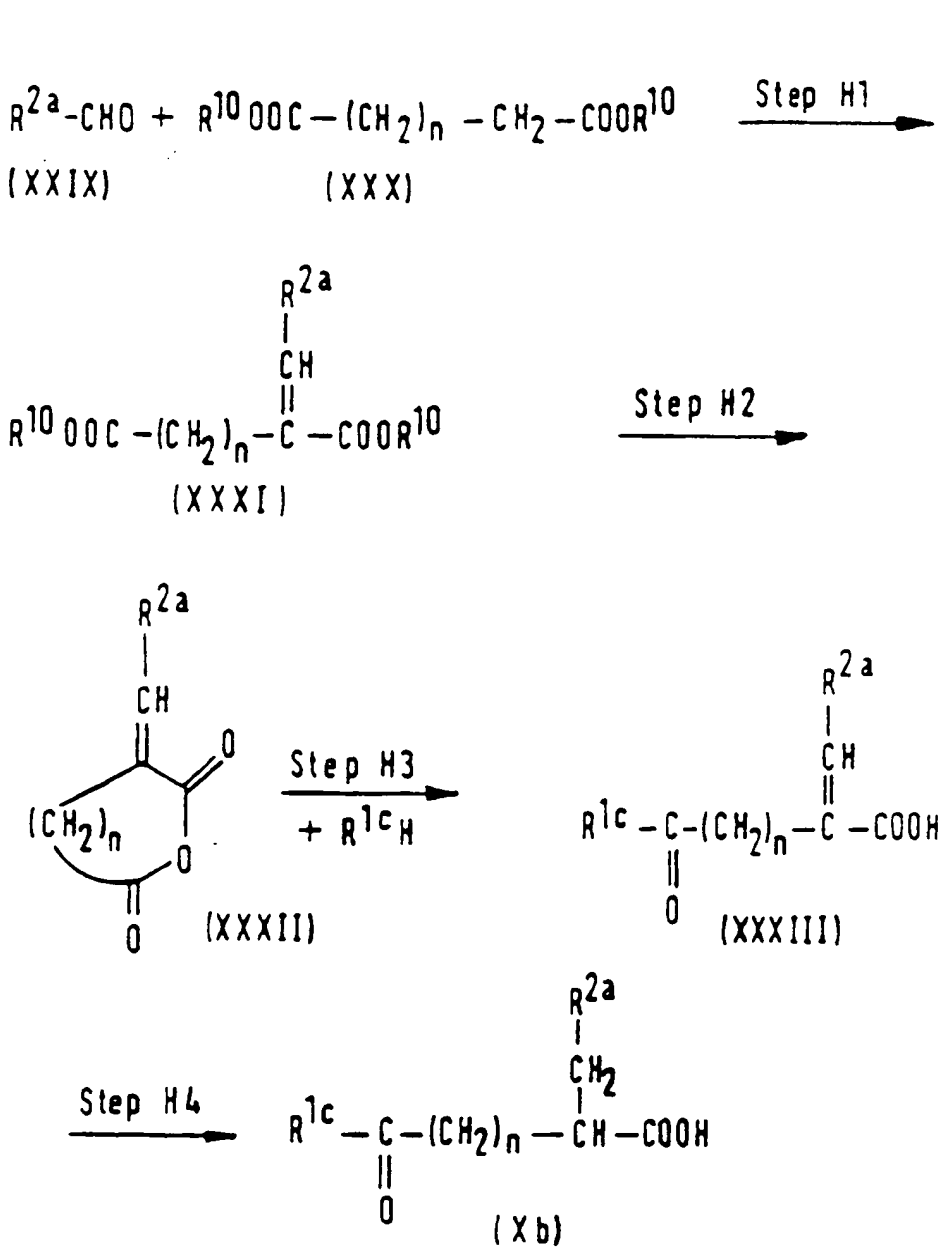
In Step F1 of this reaction scheme, the compound of formula (XXI) is first treated with a base (preferably an alkali metal hydride, such as sodium hydride) and is then reacted with a substituted methyl halide, preferably bromide, of formula (XXII), to give the compound of formula (XXIII). This is then reacted, in Step F2, with an acid (which may be a mineral acid or an organic acid, preferably hydrochloric acid), to give the alanine derivative of formula (XXIV).

Certain of the starting materials of formula (X) (Reaction Schemes B and C) can be prepared as illustrated in Reaction Schemes G, H and I:

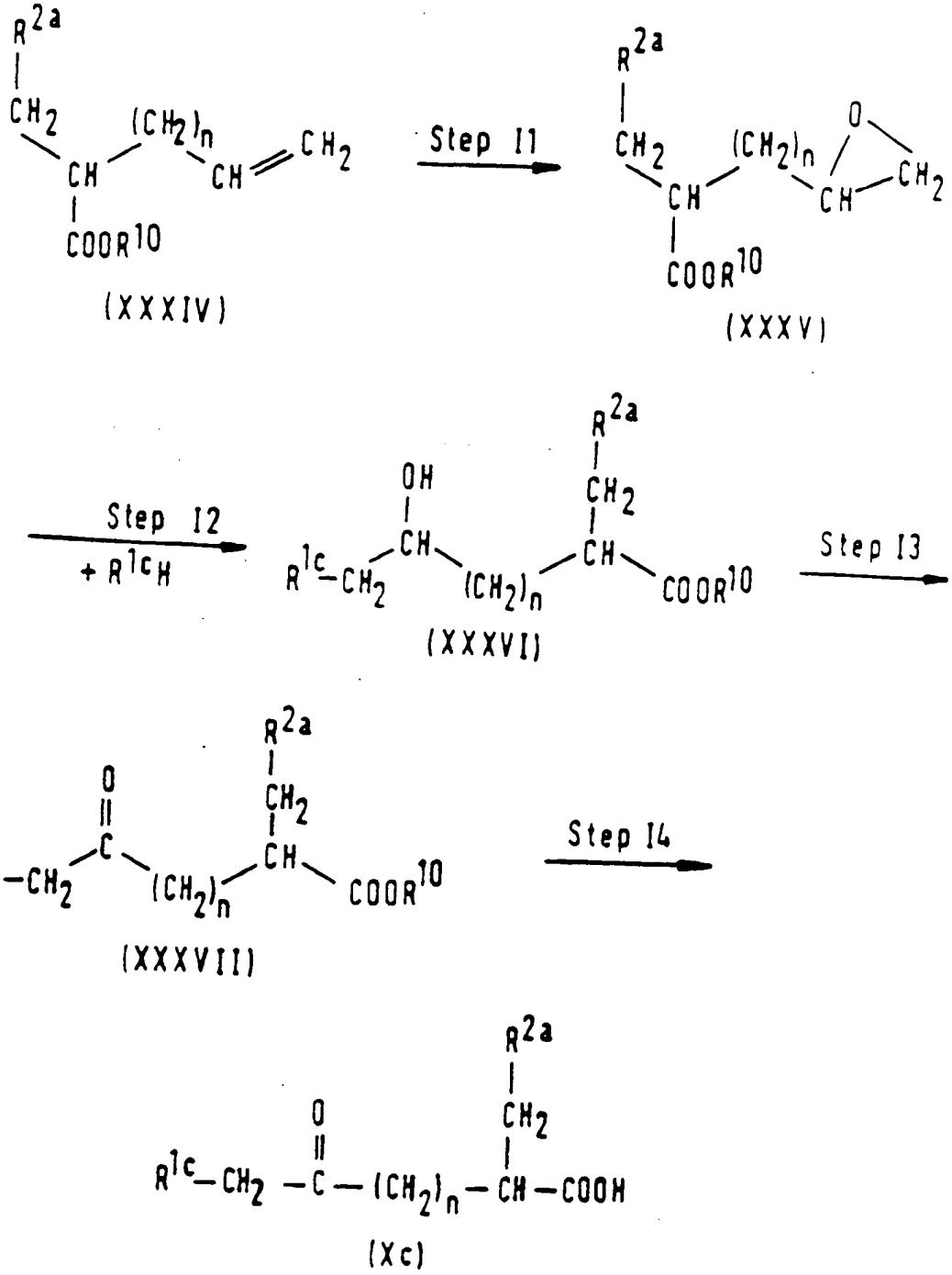
Reaction Scheme G



Reaction Scheme H

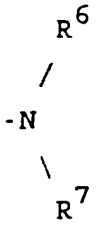


Reaction Scheme I



(XXXIV) (XXXV) (XXXVI) (XXXVII) (Xc)

In the above formulae, R^{1a}, R^{2a}, R^{10} and n are as defined above; R^{1c} represents a heterocyclic group or a group of formula (II),



(II)

in which R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, an aryl group, an aralkyl group or a C_3 - C_8 cycloalkyl group; X' and X'' each represents a halogen atom, for example the fluorine, chlorine, bromine or iodine atoms.

The reactions may be carried out as follows:

Reaction Scheme G, Step G1

In this reaction, a substituted methyl halide of formula (XXV) is reacted with a malonic acid ester of formula (XXVI). This reaction may be carried out, for example, by the method described in Organic Synthesis Coll., 3, 705.

Step G2

In this step, the mono-substituted malonic acid ester of formula (XXVII) obtained as described in Step G1 is reacted with a halide of formula (XXVIIa), to give the corresponding di-substituted malonic acid ester of formula (XXVIII), for example by the same method as in Step G1.

Step G3

In this step, the di-substituted malonic acid ester of formula (XXVIII) is subjected to hydrolysis and decarboxylation, to give the desired compound of formula (Xa). This reaction may be carried out by conventional means well known in this art.

Reaction Scheme H, Step H1

This reaction scheme prepares a compound of formula (X) in which R^1 represents a heterocyclic group or a group of formula (II), i.e. the group defined as R^{1c}. In the first step of this reaction, an aldehyde of formula (XXIX) is reacted with a glutaric acid diester or adipic acid diester of formula (XXX), to give the compound of formula (XXXI).

Step H2

In this step, the compound of formula (XXXI) is subjected to hydrolysis by conventional means to remove the protecting group R^{10} and is then heated in the presence of acetic anhydride, to afford the acid anhydride of formula (XXXII).

Step H3

The anhydride of formula (XXXII) is reacted with an amine of formula $R^{1c}H$, to cause ring opening and give the compound of formula (XXXIII).

Step H4

Finally, the compound of formula (XXXIII) is subjected to catalytic hydrogenation, which may take plac under atmosph ric pressure in th presence of a suitable catalyst, e.g. palladium-on-carbon or platinum black, to giv the d sired compound of formula (Xb).

Reaction Scheme I Step I1

In this reaction scheme, there is prepared a compound of formula (X) in which R^1 represents a methyl group substituted by a heterocyclic group or substituted by a group of formula (II), as defin d above, i.e. a group of formula R^{1c}-CH_2- (in which R^{1c} is as defined above).

In the first step of this reaction scheme, the compound of formula (XXXIV) is reacted with an oxidizing agent to give the epoxide of formula (XXXV). The oxidation is preferably effected with an organic peracid, such as 3-chloroperbenzoic acid.

The starting material of formula (XXXIV) may be prepared by reacting a propionic acid ester of formula $R^{2a}CH_2CH_2COOR^{10}$ (in which R^{2a} and R^{10} are as defined above) with an alkenyl halide of formula $CH_2=CH-(CH_2)_n-Y$ (in which n is as defined above and Y represents a halogen atom, e.g. as defined for X'). Suitable alkenyl halides include, for example, allyl chloride or allyl bromide. The reaction is preferably effected in the presence of a metallic base, such as lithium diisopropylamide, butyllithium, metallic sodium or sodium hydride.

Step I2

In this step, the epoxide of formula (XXXV) is reacted with an amine of formula $R^{1c}H$, to give the compound of formula (XXXVI). The reaction may take place under conditions similar to those employed in Step E2, except that, in this case, the presence of a base is not necessary.

Step I3

In this step, the compound of formula (XXXVI) is oxidized, using an oxidizing agent such as a sulphur trioxide/pyridine complex, pyridinium chlorochromate or pyridinium dichromate, to give the compound of formula (XXXVII).

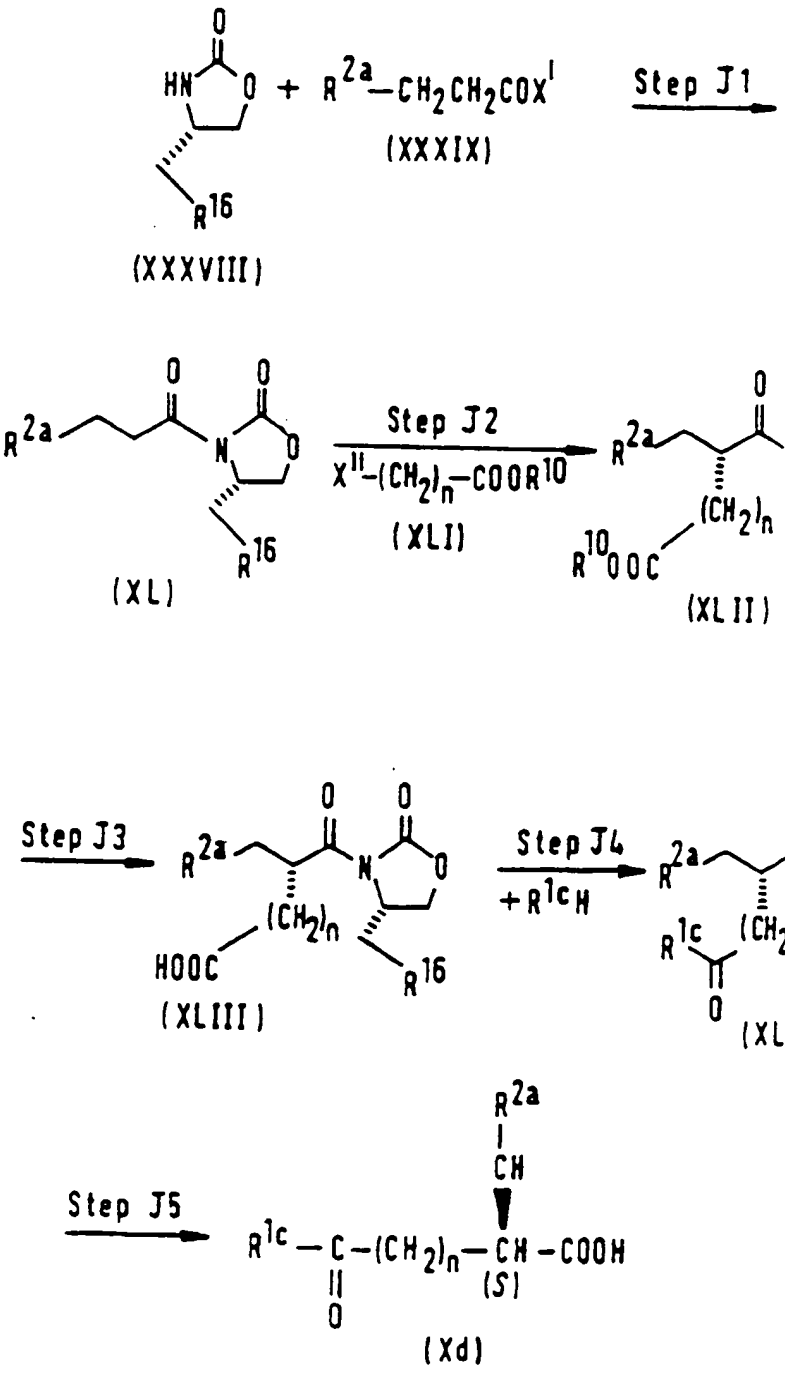
Step I4

Finally, if necessary, the carboxy-protecting group R^{10} is removed from the compound of formula (XXXVII), to give the compound of formula (Xc).

The compounds prepared in Reaction Schemes G, H and I are mixtures of isomers and, if desired, these may be used as such in the subsequent reactions (e.g. those of Reaction Schemes A - F), or the individual isomers can be separated and recovered using conventional techniques, for example, the various chromatography techniques, such as column chromatography, prior to use in the subsequent reactions.

However, if desired, the compounds of formula (X) can be synthesised stereospecifically, using the methods shown in Reaction Scheme J:

Reaction Scheme J



In the above formula, R^{1c}, R^{2a}, R^{10}, X', X'' and n are as defined above; and R^{16} represents a phenyl group or a substituted phenyl group, having at least one substituent selected from substituents (a):

Substituents (a):

C_1 - C_6 alkyl groups, C_1 - C_4 alkoxy groups, C_1 - C_7 aliphatic carboxylic acyl groups, C_1 - C_7 aliphatic carboxylic acyloxy groups, aromatic carboxylic acyl groups, aromatic carboxylic acyloxy groups, C_1 - C_7 aliphatic carboxylic acylamino groups, aromatic carboxylic acylamino groups, heterocyclic-carbonyl groups, provided that any such heterocyclic-carbonyl substituent is not itself substituted by a substituted heterocyclic or heterocyclic-carbonyl group, arylalkenoyl groups in which the alkenoyl part is C_3 - C_7, haloalkyl groups (such as the trifluoromethyl group), halogen atoms, nitro groups, cyano groups, amino groups, C_1 - C_4 alkylamino groups, dialkylamino groups in which each alkyl part is C_1 - C_4, alkylcarbamoyl groups in which the alkyl part is C_1 - C_4, dialkylcarbamoyl groups in which each alkyl part is C_1 - C_4, alkoxycarbonyloxy groups in which the alkoxy part is C_1 - C_4, heterocyclic groups, provided that any such heterocyclic substituent is not itself substituted by a substituted heterocyclic or heterocyclic-carbonyl group, carboxy groups and esters and amides of said carboxy groups, the aromatic parts of said aromatic acyl, acyloxy and acylamino groups being C_6 - C_{10} carbocyclic aryl groups which are unsubstituted or have at least one substituent selected from C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups and halogen atoms;

or a C_1 - C_6 alkyl group, e.g. a straight or branched chain alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, sec-pentyl, t-pentyl, hexyl, isohexyl, isohexyl, 2-methylbutyl and 1,2-dimethylbutyl group.

Step J1

In this step, the compound of formula (XXXVIII) is treated with a base (especially a base containing an alkali metal, such as butyllithium), to afford an alkali metal salt, which is then reacted with the halogen compound of formula (XXXIX) to give the compound of formula (XL).

Step J2

The compound of formula (XL) is converted to an alkali metal salt by reaction with a metal-containing base (e.g. lithium diisopropylamide), and is then reacted stereospecifically with the compound of formula (XLI), to give the compound of formula (XLII).

Step J3

In this step, the compound of formula (XLII) is subjected to catalytic hydrogenation (e.g. hydrogenation in the presence of a palladium-on-carbon catalyst) or to hydrolysis to remove the protecting group R^{10} and give the compound of formula (XLIII).

Step J4

The compound of formula (XLIII) is reacted with an amine of formula $R^{1c}H$, in the presence of a condensing agent (e.g., diethyl cyanophosphonate and triethylamine), to give the compound of formula (XLIV).

Step J5

Finally, this compound of formula (XLIV) is subjected to hydrolysis under conventional conditions to give the compound of formula (Xd).

INHIBITION OF RENIN ACTIVITY

The ability of various compounds of the invention to inhibit the activity of renin was determined according to the following m thod, which follows essentially the procedure of Kokubu et al. [Hypertension, 5, 191 - 197 (1983)].

Specifically, each test compound was dissolved in 60% v/v aqueous thanol. Human renin activity in the presence and absence of each compound was measured using sheep angiotensinogen. The total volume of 1 ml of assay mixtur contained 0.1 mole/litre phosphate buffer (pH 7.3), human renin (equivalent to 0.5 ng angiotensin I per ml per minute), sheep angiotensinogen (quivalent to 200 ng angiotensin I), 1 x 10^{-6} M of the test compound, 6% v/v ethanol and angiotensinas inhibitors (10 mmol /litre sodium

ethylenediamin tetraacetate and 3.4 mmole/litre 8-hydroxyquinoline). The mixture was allowed to react for 10 minutes at 37°C, and then the reaction was stopped by placing the reaction tube in a boiling water bath for 5 minutes. The mixtur was then centrifuged and the supernatant (0.05 - 0.1 ml) was used to assay remaining angiotensin I.

An identical experiment was carried out, as a control, except that the test compound was omitted. From the values obtained were calculated the % inhibition of renin activity achieved by each test compound. The results are shown in the following Table 9, in which the compounds of the invention are identified by the numbers of the Examples given hereafter in which are described their preparation. The values given are the mean of 3 or 4 experiments.

TABLE 9

Compound of Example No.	Inhibitory Activity (%)
2	91.2
3	92.2
7	96.3
17	96.7
29	97.4
34	97.7
41	98.1
42	98.6
43	98.6
44	98.0
45	98.2
46	98.4
47	98.6
48	98.3
49	98.3
50	96.0
51	98.0

As can be seen from the results in the Table above, the compounds of the present invention have a substantial inhibitory effect on the activity of human renin and are thus useful for the diagnosis and therapy of renin/angiotensin-induced hypertension in humans and other animals. Furthermore, we have found from biliary excretion and blood plasma experiments that the compounds are well absorbed from the digestive tract upon oral administration and this has been supported by tests in marmosets. Moreover, the compounds of the invention are readily soluble in water. Furthermore, in animal tests using mice and rats, the compounds of the present invention have demonstrated a lower toxicity than do the prior art compounds. All of these results indicate that the compounds of the invention will be of considerable therapeutic value and that, unlike related compounds proposed previously, they may be administered, in practice, by the oral route, as well as by the more conventional parenteral route.

The compounds of the invention may be formulated in conventional dosage forms, normally in admixture with a pharmaceutical carrier or diluent. For oral administration, the compounds can be formulated, for example, as tablets, capsules, granules, powders or syrups. For parenteral administration, they may be formulated as injections in a suitable liquid or as suppositories. The dosage will vary, depending upon the age, symptoms and body weight of the patient, as well as upon the desired end result; however, we would normally anticipate administering a dose of from 0.01 mg to 100 mg/kg body weight per day, which may be administered as a single dose or in divided doses.

The invention is further illustrated by the following non-limiting Examples. Preparation of certain of the starting mat rials employed in these Exampl s is illustrated by the subsequent Pr parations. Th biological activiti s of c rtain f the compounds of the invention are th n illustrated in th subsequ nt Experiments. In th Examples and Preparations, values of optical rotation wer measured using th sodium D-line, i.e. all are $[\alpha]_D$. Also, where an Rf value is given in these Examples and Pr parations in relation to a product, it was det rmined by thin layer chromatography on silica gel, using a 10 : 1 by volume mixture of methylene chloride and methanol as the developing solvent, unl ss otherwise specified.

EXAMPLE 1

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

1(a) N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide

0.16 ml (1.05 mmole) of diethyl cyanophosphonate (95%, i.e. of a purity about 95%) and 0.44 ml (3.15 mmole) of triethylamine were added to a solution of 261 mg (0.96 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine and 384 mg (0.96 mmole) of cyclostatin-(2-morpholinoethyl)amide dihydrochloride [prepared as described in Preparation 9(b)] dissolved in 10 ml of anhydrous tetrahydrofuran under an atmosphere of nitrogen, whilst ice-cooling. The reaction mixture was then stirred at the same temperature for 2 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by thin layer chromatography on a silica gel plate (developing solvent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 450 mg (81%) of the title compound as white crystals, melting at 73 - 75°C.
Mass Spectrum m/e: 582 (M^+ + 1).

1(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

A solution of 310 mg (0.53 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 1(a) above] in 5 ml of a 4N solution of hydrogen chloride in dioxane was stirred at room temperature for 30 minutes, after which the solvent was removed by distillation under reduced pressure. The residue was dried thoroughly, after which it was suspended in 10 ml of anhydrous tetrahydrofuran. 192 mg (0.59 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)-propionic acid (prepared as described in Preparation 4) were then added to the resulting solution. 0.09 ml (0.59 mmole) of diethyl cyanophosphonate (95%) and 0.36 ml (2.58 mmole) of triethylamine were then added to this mixture, whilst ice-cooling and under an atmosphere of nitrogen, and the reaction mixture was stirred whilst continuing the ice-cooling for 2 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by thin layer chromatography on a silica gel plate (developing solvent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 220 mg (52%) of the title compound, melting at 93 - 96°C.

Elemental analysis:

	Calculated for $C_{42}H_{58}O_7N_6S \cdot H_2O$:							
Found:	C,	62.35%;	H,	7.47%;	N,	10.39%;	S,	3.96%.
	C,	62.33%;	H,	7.34%;	N,	10.09%;	S,	3.76%.

EXAMPLE 2

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

2(a) N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide

A solution of 314 mg (0.74 mmole) of N-(t-butoxycarbony1)-cyclostation-(2-morpholinoethyl)amide [prepared by a proc dure similar to that d scrib d in Pr parati n 9(a)] in 5 m1 of a 4N solution f hydrog n chloride in dioxane was agitated at room temperatur for 30 minutes. At the nd of this time, the solv nt was removed by distillation und r reduced pr ssur . Diethyl ether was added to th r sidue, and then th solv nt was again r moved by distillation und r reduced pr ssure. The residue was dried thoroughly and suspended, together ith 200 mg (0.73 mmole) of N-(t-butoxycarbony1)-(4-thiazolyl)-DL-alanine, in 10 ml of anhydrous tetrahydrofuran. 0.13 ml (0.86 mmole) of diethyl cyanophosphonate (95%) and 0.34 ml (2.44 mmole) of triethylamin were then added t this suspension, whilst ice-cooling and under an atmosph r of

nitrogen. The mixture was then stirred whilst continuing the ice-cooling for 2 hours. At the end of this time, th solvent was removed by distillation under reduced pressure, and the residue was purified by thin layer chromatography on a silica gel plat (developing solvent: a 10 : 1 by volum mixture of chloroform and methanol), to afford 404 mg (95%) of th title compound as white crystals, melting at 73 - 75°C.
Mass Spectrum m/e: 582 (M^+ + 1).

Elemental analysis:

	Calculated for $C_{28}H_{47}N_5O_6S \cdot H_2O$:							
Found:	C,	56.07%;	H,	8.23%;	N,	11.68%;	S,	5.34%.
	C,	56.31%;	H,	7.96%;	N,	11.41%;	S,	5.70%.

2(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

A solution of 280 mg (0.48 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 2(a) above] dissolved in 5 ml of a 4N solution of hydrogen chloride in dioxane was stirred at room temperature for 30 minutes. At the end of this time, the solvent was removed by distillation under reduced pressure. The residue was dried thoroughly, after which it was suspended in 10 ml of anhydrous tetrahydrofuran. 173 mg (0.53 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionic acid (prepared as described in Preparation 4) were then added to the resulting solution, after which 0.09 ml (0.59 mmole) of diethyl cyanophosphonate (95%) and 0.34 ml (2.44 mmole) of triethylamine were added to the mixture, whilst ice-cooling and under an atmosphere of nitrogen. The reaction mixture was then stirred whilst continuing the ice-cooling for 2 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by thin layer chromatography on a silica gel plate (developing solvent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 175 mg (46%) of the title compound, melting at 92 - 95°C.

Elemental analysis:

	Calculated for $C_{42}H_{58}N_6O_7S \cdot H_2O$:							
Found:	C,	62.35%;	H,	7.47%;	N,	10.39%;	S,	3.96%.
	C,	61.98%;	H,	7.25%;	N,	10.08%;	S,	3.77%.

EXAMPLE 3

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

3(a) N-[N-(t-Butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 0.125 g (0.29 mmole) of N-(t-butoxycarbonyl)-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Preparation 9(a)] in 5 ml of dioxane, whilst ice-cooling, and the mixture was then stirred at room temperature for 2 hours. At the end of this time, the reaction mixture was vaporated to dryn ss under reduced pr ssure. A solution of 89 mg (0.348 mmole) of N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanin (prepared as described in Preparation 8) dissolved in 15 ml of dimethylformamide was then added to th resulting residue. 0.13 g (12.76 mmole) of triethylamine and 57 mg (0.348 mmol) of diethyl cyanophosphonate (95%) were added to th mixtur , whilst stirring, and the mixture was allowed to react at room temperature for 21 hours. At the end of this tim , the solvent was removed by distillation under reduced pressure. Wat r was added to th residue, and th mixtur was extracted with methylene chloride. The extract was dried, and the solvent was r moved by

distillation under reduced pressure. The residue was purified by column chromatography through silica gel, using a 1 : 49 by volume mixture of methanol and methylene chloride as eluent, to afford 85 mg (51.8%) of the title compound as an oily substanc .

3(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

A solution of 85 mg (0.15 mmole) of N-[N-(t-butoxy-carbonyl)-3-(5-isoxazolyl)-DL-alanyl]-cyclo statin-(2-morpholinoethyl)amide [prepared as described in Example 3(a) above] dissolved in 2 ml of a 4N solution of hydrogen chloride in dioxane was stirred at room temperature for 1.5 hours, after which the reaction mixture was evaporated to dryness under reduced pressure. The residue was suspended in tetrahydrofuran, and 49 mg (0.15 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionic acid (prepared as described in Preparation 4), 67 mg (0.66 mmole) of triethylamine and 29 mg (0.18 mmole) of diethyl cyanophosphonate (95%) were added, whilst stirring, to the resulting suspension. The mixture was then stirred at room temperature for 3 hours, after which it was allowed to stand for 4 days. The solvent was then removed by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography on a silica gel plate (developing solvent: 10% by volume methanol in methylene chloride), to afford 74 mg (61.7%) of the title compound, melting at 84 - 86 °C.

Elemental analysis:

Calculated for $C_{42}H_{57}N_6O_8 \cdot H_2O$:						
	C,	63.70%;	H,	7.51%;	N,	10.61%.
Found:	C,	63.75%;	H,	7.19%;	N,	10.41%.

EXAMPLE 4

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(2-thienyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

4(a) N-[N-(t-Butoxycarbonyl)-3-(2-thienyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 2(a), 200 mg (0.74 mmole) of N-(t-butoxycarbonyl)-3-(2-thienyl)-DL-alanine (prepared by a procedure similar to that described in Preparation 8) were reacted with 300 mg (0.74 mmole) of cyclostatin-(2-morpholinoethyl)amide dihydrochloride [prepared as described in Preparation 9(b)], to afford 310 mg of the title compound as a colourless amorphous substance.

Elemental analysis:

Calculated for $C_{29}H_{48}N_4O_6S$:								
	C,	59.97%;	H,	8.33%;	N,	9.65%;	S,	5.52%.
Found:	C,	59.50%;	H,	8.18%	N,	9.62%;	S,	5.68%.

4(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(2-thienyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

A procedure similar to that described in Example 2(b) was r p sted, except that 70 mg (0.12 mmole) of N-[N-(t-butoxycarbonyl)-3-(2-thienyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide {instead of th N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide, and prepared in a manner similar to that described in Pr paration 8} w re r acted with 40 mg (0.12 mmol) of (2R)-3-morpholinocar-

bonyl-2-(1-naphthylmethyl)propionic acid, to afford 27 mg of the title compound as a colourless amorphous substance.

Silica gel thin layer chromatography, Rf value 0.59.

Elemental analysis:

Calculated for $C_{43}H_{59}N_5O_7S \cdot 2.5\ H_2O$:								
Found:	C,	61.85%;	H,	7.73%;	N,	8.39%;	S,	3.84%.
	C,	61.74%;	H,	7.50%;	N,	8.18%;	S,	3.62%.

EXAMPLE 5

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-L-histidyl}-cyclostatin-(2-morpholinoethyl)-amide

Following a procedure similar to that described in Example 3(a), 344 mg (0.84 mmole) of N-(t-butoxycarbonyl)-N^{im}-tosyl-L-histidine were reacted with 300 mg (0.70 mmole) of N-(t-butoxycarbonyl)-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Preparation 9(a)], to afford 240 mg of N-[N-(t-butoxycarbonyl)-N^{im}-tosyl-L-histidyl]-cyclostatin-(2-morpholinoethyl)amide as white crystals.

Then, following a procedure similar to that described in Example 1(b), 220 mg (0.31 mmole) of the N-[N-(t-butoxycarbonyl)-N^{im}-tosyl-L-histidyl]-cyclostatin-(2-morpholinoethyl)amide (prepared as described above) were allowed to react with 100 mg (0.31 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)-propionic acid (prepared as described in Preparation 4) for 15 hours. At the end of this time, a solution of 83 mg (0.61 mmole) of 1-hydroxybenzotriazole in methanol was added, and the mixture was stirred at room temperature for 1 hour. The solvent was then removed by distillation under reduced pressure. The residue was purified by preparative thin layer chromatography on a silica gel plate (developing solvent: an 8 : 1 by volume mixture of methylene chloride and methanol), to afford 50 mg of the 2.5-hydrate of the title compound as white crystals, melting at 105 - 109°C.

Elemental analysis:

Calculated for $C_{42}H_{59}N_7O_7 \cdot 2.5\ H_2O$:						
Found:	C,	61.59%;	H,	7.88%;	N,	11.97%.
	C,	61.65%;	H,	7.65%;	N,	11.73%.

EXAMPLE 6

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-L-leucyl}-cyclostatin-(2-morpholinoethyl)-amide

Following a procedure similar to that described in Example 1(b), 122 mg (0.373 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionic acid (prepared as described in Preparation 4) were reacted with 200 mg (0.370 mmole) of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-(2-morpholinoethyl)-amide [prepared by a procedure similar to that described in Example 1(a)], to afford 154 mg of the title compound as a pale yellow amorphous substanc .

Silica g l thin layer chromatography, Rf value 0.44.

Elemental analysis:

Calculated for $C_{42}H_{63}N_5O_7 \cdot 2.5\ H_2O$:						
Found:	C,	64.18%;	H,	8.59%;	N,	8.91%.
	C,	63.82%;	H,	8.31%;	N,	8.81%.

EXAMPLE 7

N-{N-[(2R)-2-(1-Naphthylmethyl)-3-(4-phenyl-1-piperazinylcarbonyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpolinoethyl)amide

Following a procedure similar to that described in Example 2(b), 90 mg (0.22 mmole) of (2R)2-(1-naphthylmethyl)-3-(4-phenyl-1-piperazinylcarbonyl)propionic acid (prepared by a procedure similar to that described in Preparation 10) were reacted with 130 mg (0.22 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 2(a)], to afford 103 mg of the monohydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.52.

Elemental analysis:

Calculated for $C_{48}H_{63}N_7O_6S \cdot H_2O$:								
Found:	C,	65.21%;	H,	7.41%;	N,	11.09%;	S,	3.63%.
	C,	65.36%;	H,	7.51%;	N,	11.22%;	S,	3.39%.

EXAMPLE 8

N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 1(b), 125 mg (0.35 mmole) of (2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionic acid (prepared as described in Preparation 14) were reacted with 200 mg (0.34 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 2(a)], to afford 214 mg (75%) of the monohydrate of the title compound, melting at 82 - 86 °C

Elemental analysis:

Calculated for $C_{46}H_{62}N_6O_6S \cdot H_2O$:								
Found:	C,	65.38%;	H,	7.63%;	N,	9.94%;	S,	3.79%.
	C,	65.30%;	H,	7.53%;	N,	9.94%;	S,	3.90%.

EXAMPLE 9

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amid

9(a) N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

Following a procedure similar to that described in Example 3(a), 1.0 g (2.3 mmole) of N-(t-butoxycarbonyl)-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide [prepared by a procedure similar to that described in Preparation 9(a)] was reacted with 0.63 g (2.3 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, to afford 1.08 g of the title compound as an oil.

9(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

Following a procedure similar to that described in Example 1(b), 207 mg (0.35 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide [prepared as described in Example 9(a) above] were reacted with 115 mg (0.35 mmole) of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionic acid (prepared as described in Preparation 4), to afford 207 mg of the dihydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.53.

Elemental analysis:

Calculated for $C_{43}H_{58}N_6O_7S \cdot 2\,H_2O$:								
Found:	C,	61.55%;	H,	7.45%;	N,	10.02%;	S,	3.82%.
	C,	61.74%;	H,	7.43%;	N,	9.77%;	S,	3.97%.

EXAMPLE 10

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide

10(a) N-(t-Butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide

Following a procedure similar to that described in Preparation 9, 0.33 g (3.81 mmole) of (S)-2-methylbutylamine (instead of 2-morpholinoethylamine) were reacted with 1.00 g (3.17 mmole) of N-(t-butoxycarbonyl)cyclostatin, to afford 1.13 g (93%) of the title compound as a white powder.

10(b) N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[-(S)-2-methylbutyl]amide

Following a procedure similar to that described in Example 1(a), 0.50 g (1.30 mmole) of N-(t-butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide [prepared as described in Example 10(a)] were reacted with 354 mg (1.30 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, and the product was worked-up according to Example 1(b), to give 211 mg (61%) of the monohydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.63.

Elemental analysis:

Calculated for $C_{41}H_{57}N_5O_6S \cdot H_2O$:								
	C,	64.29%;	H,	7.76%;	N,	9.14%;	S,	4.19%.
Found:	C,	63.99%;	H,	7.56%;	N,	9.20%;	S,	4.01%.

EXAMPLE 11

N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide

Following a procedure similar to that described in Example 1(a), 330 mg (1.3 mmole) of N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanine [instead of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine] were reacted with the compound prepared by cleaving the t-butoxycarbonyl group from 500 mg (1.3 mmole) of N-(t-butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide, and the product was worked-up according to Example 1(b), to give 170 mg of the 2.5-hydrate of the title compound as white crystals, melting at 68 - 72°C.

Elemental analysis:

Calculated for $C_{41}H_{57}N_5O_7 \cdot 2.5\ H_2O$:						
	C,	63.38%;	H,	8.04%;	N,	9.01%.
Found:	C,	63.41%;	H,	7.79%;	N,	8.81%.

EXAMPLE 12

N-{N-[5-(N-Benzyl-N-methylamino)-2-(1-naphthylmethyl)-4-oxopentanoyl]-L-leucyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 1(b), 210 mg (0.559 mmole) of 5-(N-benzyl-N-methylamino)-2-(1-naphthylmethyl)-4-oxopentanoic acid (prepared as described in Preparation 13) were reacted with 300 mg (0.555 mmole) of N-(t-butoxycarbonyl)-L-leucyl-cyclostatin-(2-morpholinoethyl)amide [prepared by a procedure similar to that described in Example 2(a)], to afford 141 mg of the tetrahydrate of the title compound as a pale brown amorphous substance.

Silica gel thin layer chromatography, Rf value 0.47.

Elemental analysis:

Calculated for $C_{47}H_{67}N_5O_6 \cdot 4\ H_2O$:						
	C,	64.88%;	H,	8.69%;	N,	8.05%.
Found:	C,	65.14%;	H,	8.59%;	N,	8.02%.

EXAMPLE 13

N-{N-[5-(N-Benzyl-N-methylamino)-2-(1-naphthylmethyl)-4-oxopentanoyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 1(b), 130 mg (0.346 mmole) of 5-(N-benzyl-N-methylamino)-2-(1-naphthylmethyl)-4-oxopentanoic acid (prepared as described in Preparation 13) were reacted with 200 mg (0.344 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-cyclostatin-(2-morpholinoethyl)amide, to afford 26 mg of the trihydrate of the title compound as a pale brown amorphous substance.

Silica gel thin layer chromatography, Rf value 0.42.

Elemental analysis:

Calculated for $C_{47}H_{62}N_6O_6S \cdot 3\,H_2O$:								
Found:	C,	63.20%;	H,	7.67%;	N,	9.41%;	S,	3.59%.
	C,	63.36%;	H,	7.55%;	N,	9.31%;	S,	3.23%.

EXAMPLE 14

N-{N-[(2R)-4-Morpholinocarbonyl-2-(1-naphthylmethyl)butanoyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 1(a), 249 mg (0.73 mmole) of 4-morpholinocarbonyl-2-(1-naphthylmethyl)butyric acid (prepared as described in Preparation 11) [instead of (2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionic acid] were reacted with 384 mg (0.66 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-cyclostatin-(2-morpholinoethyl)amide. The thin layer chromatogram of the products showed two main spots. The compound detected as the lower spot on the chromatogram was purified by silica gel thin layer chromatography (developing solvent: an 8 : 1 by volume mixture of methylene chloride and methanol), to afford 110 mg of the monohydrate of the title compound as white crystals, melting at 87 - 90 °C.

Silica gel thin layer chromatography, Rf value 0.58.

$[\alpha]_D^{25}$ = -24.4° (c = 0.5, methanol).

Elemental analysis:

Calculated for $C_{43}H_{60}N_6O_7S \cdot H_2O$:								
Found:	C,	62.73%;	H,	7.59%;	N,	10.21%;	S,	3.89%.
	C,	62.95%;	H,	7.76%;	N,	9.90%;	S,	4.10%.

EXAMPLE 15

N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a proc dure similar to that described in Example 3(b), 100 mg (0.28 mmol) of (2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionic acid (pr pared as described in Pr paration 14) were reacted with 160 mg (0.28 mmole) of N-[N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amid , to afford 56 mg of th dihydrate of the title compound as a colourless amorphous substance.

Silica gel thin lay r chromatography, Rf value 0.41.

Elemental analysis:

Calculated for $C_{46}H_{60}N_6O_7 \cdot 2\,H_2O$:						
	C,	65.38%;	H,	7.63%;	N,	9.95%.
Found:	C,	65.40%;	H,	7.38%;	N,	9.94%.

EXAMPLE 16

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)-amide

16(a) N-{N-[N-(t-Butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

The t-butoxycarbonyl group was removed from 254 mg (0.44 mmole) of N-[N-t-butoxycarbonyl-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-2-(morpholinoethyl)amide [prepared as described in Example 2(a)] using a 4N solution of hydrogen chloride in dioxane. The product was then suspended, together with 165 mg (0.52 mmole) of N-(t-butoxycarbonyl)-3-(1-naphthylmethyl)-L-alanine, in 10 ml of anhydrous tetrahydrofuran, and 0.08 ml (0.53 mmole) of diethyl cyanophosphonate (95%) and 0.27 ml (1.94 mmole) of triethylamine were added to the suspension under an atmosphere of nitrogen, whilst ice-cooling. The mixture was agitated at room temperature overnight, after which the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 7 : 1 by volume mixture of chloroform and methanol), to afford 303 mg (87%) of the dihydrate of the title compound as white crystals, melting at 113 - 116°C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_7S \cdot 2\,H_2O$:								
	C,	60.42%;	H,	7.67%;	N,	10.31%;	S,	3.93%.
Found:	C,	60.60%;	H,	7.43%;	N,	10.09%;	S,	3.97%.

16(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

The t-butoxycarbonyl group was removed from 262 mg (0.34 mmole) of N-{N-[N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 16(a)] using a 4N solution of hydrogen chloride in dioxane. The product, together with 59 mg (0.40 mmole) of 1-morpholinoacetic acid, was suspended in 5 ml of anhydrous tetrahydrofuran, and 0.06 ml (0.40 mmole) of diethyl cyanophosphonate (95%) and 0.21 ml (1.51 mmole) of triethylamine were added to the suspension, whilst ice-cooling in an atmosphere of nitrogen. The mixture was agitated at room temperature overnight, and then the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 7 : 1 by volume mixture of chloroform and methanol), to afford 230 mg (85%) of the dihydrate of the title compound as white crystals, melting at 98 - 99°C.

Elemental analysis:

Calculated for $C_{42}H_{59}N_7O_7S \cdot 2\ H_2O$:								
	C,	59.90%;	H,	7.54%;	N,	11.64%;	S,	3.81%.
Found:	C,	59.69%;	H,	7.61%;	N,	11.50%;	S,	3.74%.

EXAMPLE 17

N-{N-[N-(4-Morpholinobutyryl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 16(b), 200 mg (0.26 mmole) of N-{N-[N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 16(a)] and 61 mg (0.29 mmole) of 4-morpholinobutyric acid were reacted, to afford 100 mg of the 1.5-hydrate of the title compound as a white power.

Silica gel thin layer chromatography, Rf value 0.27.

Elemental analysis:

Calculated for $C_{44}H_{63}N_7O_7S \cdot {}^3/_2\ H_2O$:								
	C,	61.37%;	H,	7.73%;	N,	11.39%;	S,	3.72%.
Found:	C,	61.19%;	H,	7.65%;	N,	11.22%;	S,	3.60%.

EXAMPLE 18

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)-amide

18(a) N-{N-[N-Bromoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 350 mg (0.45 mmole) of N-{N-[N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 16(a)] in 5 ml of methanol, and the mixture was agitated at room temperature for 1 hour. At the end of this time, the reaction mixture was concentrated by distillation under reduced pressure, and the residue was suspended in 10 ml of tetrahydrofuran. 0.085 g (0.54 mmole) of bromoacetyl chloride and 0.165 g (1.62 mmole) of triethylamine were then added to this suspension, whilst ice-cooling, and the mixture was agitated for 3 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of chloroform and methanol), to afford 122 mg of the dihydrate of the title compound as white crystals, melting at 96 - 100°C.

Elemental analysis:

Calculated for $C_{38}H_{51}N_6O_6SBr \cdot 2\ H_2O$:						
	C,	54.60%;	H,	6.63%;	N,	10.05%.
Found:	C,	54.83%;	H,	6.36%;	N,	9.89%.

18(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

0.026 g (0.3 mmole) of morpholine was added, whilst ice-cooling, to a suspension of 100 mg (0.12 mmole) of N-{N-[N-bromoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in step (a) above] in 5 ml of dimethylformamide, and the mixture was agitated at room temperature overnight. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of chloroform and methanol), to afford 52 mg of the dihydrate of the title compound as crystals, melting at 96 - 99 °C.

Elemental analysis:

Calculated for $C_{42}H_{59}N_7O_7S \cdot 2\,H_2O$:								
Found:	C,	59.90%;	H,	7.54%;	N,	11.64%;	S,	3.81%.
	C,	59.69%;	H,	7.61%;	N,	11.50%;	S,	3.74%.

EXAMPLE 19

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amide

19(a) N-[N-(t-Butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added, whilst ice-cooling, to a solution of 0.125 g (0.29 mmole) of N-(t-butoxycarbonyl)-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Preparation 9(a)] in 5 ml of dioxane, and the mixture was agitated at room temperature for 2 hours. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure, and a solution of 89 mg (0.348 mmole) of N-(t-butoxycarbonyl)-(5-isoxazolyl)-L-alanine (prepared as described in Preparation 8) in 15 ml of dimethylformamide was added to the residue. 0.13 g (1.276 mmole) of triethylamine and 57 mg (0.348 mmole) of diethyl cyanophosphonate (95%) were then added to the mixture, which was then allowed to react at room temperature for 21 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and water was added to the residue. The mixture was then extracted with methylene chloride, the extract was dried, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 1 : 49 by volume mixture of methanol and methylene chloride), to afford 85 mg (51.8%) of the title compound as an oily substance.

19(b) N-{N-[N-(t-Butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 0.2 g (0.35 mmole) of N-[N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in step (a) above] in 5 ml of methanol, and the mixture was agitated at room temperature for 1 hour. At the end of this time, methanol and dioxane were removed by distillation to dryness under reduced pressure, and the residue was suspended in anhydrous tetrahydrofuran. 0.11 g (0.35 mmole) of N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanine, 0.14 g (1.4 mmole) of triethylamine and 69 mg (0.42 mmole) of diethyl cyanophosphonate (95%) were added to this suspension, whilst ice-cooling, and the mixture was agitated at the temperature of ice-cooling for 0.5 hours and then at room temperature for 39 hours. At the end of this time, the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 1 : 9 by volume mixture of methanol and methylene chloride), to afford 0.19 g (70.4%) of the 2.5-hydrate of the title compound as a colourless amorphous substance.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_8 \cdot 2.5\ H_2O$:						
Found:	C,	60.95%;	H,	7.86%;	N,	10.40%.
	C,	60.76%;	H,	7.67%;	N,	10 36%.

19(c) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

2 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 90 mg (0.118 mmole) of N-{N-[N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide in 2 ml of methanol, and the mixture was agitated at room temperature for 1 hour. The reaction mixture was then suspended in 15 ml of anhydrous tetrahydrofuran, and 17 mg (0.118 mole) of 1-morpholinoacetic acid, 48 mg (0.472 mmole) of triethylamine and 23 mg (0.142 mmole) of diethyl cyanophosphonate (95%) were added to the resulting suspension, whilst ice-cooling. The mixture was then agitated at the temperature of ice-cooling for 0.5 hours and then at room temperature for a further 14 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 1 : 9 by volume mixture of methanol and methylene chloride), to afford 33 mg (33.8%) of the dihydrate of the title compound as a pale-yellow powder, melting at 75 - 77 °C.

Elemental analysis:

Calculated for $C_{42}H_{59}N_7O_8 \cdot 2\ H_2O$:						
Found:	C,	61.07%;	H,	7.69%;	N,	11.87%.
	C,	61.16%;	H,	7.47%;	N,	11.96%.

EXAMPLE 20

N-{N-[N-(4-Phenyl-1-piperazinylacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

20(a) N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide

3 g of cyclostatin-(2-morpholinoethyl)amide dihydrochloride, 2.04 g of N-(t-butoxycarbonyl)-(4-thiazolyl)-DL-alanine and 4.2 ml of triethylamine were added to 50 ml of dimethylformamide, and then 1.34 g of diethyl cyanophosphonate (90%) was added dropwise to the mixture, whilst ice-cooling. The reaction mixture was agitated for 6 hours, and then allowed to stand overnight. It was then evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride, and the resulting solution was washed with a saturated aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 1 : 19 by volume mixture of methanol and methylene chloride), to afford 2.80 g of the title compound as a white crystalline substance, melting at 72 - 75 °C.

20(b) N-{N-[N-(4-Phenyl-1-piperazinylacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

279 mg of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide and 2 ml of a 4N solution of hydrogen chloride in di xane were added to 2 ml of methanol, and th mixture was agitated at room temperatur for 1 hour. At the nd of this time, it was concentrated by evaporation under

reduced pressure. The residue was dissolved in 5 ml of dimethylformamide, and 200 mg of N-(4-phenyl-1-piperazinylacetyl)-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 16), 0.33 ml of triethylamine and 100 mg of diethyl cyanophosphonate (90%) were added thereto, whilst ice-cooling. The mixture was then agitated for 4 hours, after which it was concentrated by evaporation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 1 : 19 by volume mixture of methanol and methylene chloride), to afford 233 mg of the 2.5-hydrate of the title compound as a colourless amorphous substance.

Silica gel thin layer chromatography, Rf value 0.53.

Elemental analysis:

Calculated for $C_{48}H_{64}N_8O_6S \cdot 2.5\ H_2O$:								
Found:	C,	62.25%;	H,	7.51%;	N,	12.10%;	S,	3.46%.
	C,	62.48%;	H,	7.52%;	N,	11.97%;	S,	3.67%.

EXAMPLE 21

N-{N-[N-Diethylaminoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

21(a) Methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate

1.11 g (11.1 mmole) of triethylamine and 1.02 g (5.5 mmole) of bromoacetyl chloride were added to a mixture of 1.3 g (5 mmole) of methyl 3-(1-naphthyl)-L-alanate in 30 ml of methylene chloride whilst cooling and stirring, and the mixture was then stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was dried, the solvent was removed by distillation, and the residue was crystallized from a mixture of ethyl acetate and hexane, to afford 1.5 g of the title compound, melting at 110°C.

21(b) Methyl N,N-diethylaminoacetyl-3-(1-naphthyl)-L-alanate

63.6 mg (0.6 mmole) of sodium carbonate and 87.8 mg (1.2 mmole) of diethylamine were added to a solution of 350 mg (1 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in step (a) above] in 10 ml of dimethylformamide, and the mixture was agitated at room temperature for 10 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, a small amount of water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was dried, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 319 mg of the title compound as an oily substance.

21(c) N-{N-[N,N-Diethylaminoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

1 ml of a 1N aqueous solution of sodium hydroxide was added to a solution of 159 mg (0.465 mmole) of methyl N,N-diethylaminoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in step (b) above] in 1 ml of methanol, and the mixture was agitated at room temperature for 4 hours. 1 ml of 1N aqueous hydrochloric acid was added, and then the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 3 ml of dimethylformamide, and 47 mg (0.465 mmole) of triethylamine, 224 mg (0.465 mmole) of 3-(4-thiazolyl)-DL-alanyl-cyclostatin-(2-morpholinoethyl)amide and 75.8 mg (0.465 mmole) of diethyl cyanophosphonate (95%) were added thereto, and the reaction mixture was agitated at room temperature for 4 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 95 mg of the dihydrate of the title compound as white crystals.

Elemental analysis:

Calculated for $C_{42}H_{61}N_7O_6S \cdot 2\,H_2O$:								
	C,	60.99%;	H,	7.92%;	N,	11.85%;	S,	3.88%.
Found:	C,	61.06%;	H,	7.94%;	N,	11.94%;	S,	3.87%.

Silica gel thin layer chromatography, Rf value 0.57.

EXAMPLE 22

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 21(b), 175 mg (0.5 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in Example 21(a)] and 60.1 mg (0.5 mmole) of N-benzyl-N-methylamine were reacted together and subsequently treated as described in Example 21(c), to afford 51 mg of the sesquihydrate of the title compound as white crystals, melting at 71 - 75 °C.

Elemental analysis:

Calculated for $C_{46}H_{61}N_7O_6S \cdot 1.5\,H_2O$:								
	C,	63.71%;	H,	7.44%;	N,	11.30%;	S,	3.70%.
Found:	C,	63.70%;	H,	7.28%;	N,	11.04%;	S,	3.57%.

EXAMPLE 23

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 21(b), 175 mg (0.5 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in Example 21(a)] and 64.1 mg (0.5 mmole) of N-cyclohexyl-N-methylamine were reacted together and subsequently treated as described in Example 21-(c), to afford 65 mg of the monohydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.56.

Elemental analysis:

Calculated for $C_{45}H_{65}N_7O_6S \cdot H_2O$:								
	C,	63.58%;	H,	7.94%;	N,	11.53%;	S,	3.77%.
Found:	C,	63.67%;	H,	8.05%;	N,	11.28%;	S,	3.64%.

EXAMPLE 24

N-{N-[N-Morph linoac tyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(1-ethyl-2-pyrrolidinylm thyl)amide

A compound not within the scope of the inv ntion.

24(a) Methyl N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatinate

2 ml of thionyl chloride were added at -20 °C to 20 ml of methanol, and the mixture was agitated for 10 minutes at the same temperature (-20 °C). 2.85 g (9.0 mmole) of N-(t-butoxycarbonyl)-cyclostatin were then added to the mixture, and the mixture was agitated at room temperature for 14 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the product was distilled azeotropically three times with benzene to give methyl cyclostatinate hydrochloride. This product was then dissolved in 30 ml of dimethylformamide, and 2.71 g (9.9 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanine, 1.97 g (10.9 mmole) of diethyl cyanophosphonate (95%) and 2.76 ml (19.9 mmole) of triethylamine were added to the resulting solution, whilst ice-cooling. The mixture was then agitated at room temperature for 3 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, the residue was dissolved in ethyl acetate, the organic layer was washed with a 5% w/v aqueous solution of sodium bicarbonate, with a 5% w/v aqueous solution of citric acid and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 50 : 1 by volume mixture of methylene chloride and methanol), to afford 3.76 g of the title compound as an amorphous substance.

Elemental analysis:

Calculated for $C_{23}H_{37}N_3O_6S$:								
	C,	57.12;	H,	7.71%;	N,	8.69%;	S,	6.63%.
Found:	C,	56.87;	H,	7.75%;	N,	8.41%;	S,	6.68%.

24(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin

The t-butoxycarbonyl group was removed from 2.7 g (5.6 mmole) of methyl N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatinate [prepared as described in step (a) above] by treatment with a 4N solution of hydrogen chloride in dioxane. The hydrochloride thus obtained, together with 1.9 g (5.6 mmole) of N-morpholinoacetyl-(1-naphthyl)-L-alanine [prepared as described in Preparation 17], was dissolved in 40 ml of methylene chloride, and 1.37 g (7.6 mmole) of diethyl cyanophosphonate (95%) and 1.83 ml (13.2 mmole) of triethylamine were added to the resulting solution, whilst ice-cooling. The mixture was then agitated at room temperature for 3 hours. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was washed with a 5% w/v aqueous solution of citric acid, with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was crystallized by the addition of diethyl ether, to afford 3.8 g of methyl N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatinate (melting at 54 - 57 °C).

3.1 ml (3.1 mmole) of a 1N aqueous solution of sodium hydroxide were added to a solution of 2.2 g (3.1 mmole) of the methyl ester obtained as described above in 20 ml of methanol, and the mixture was agitated at room temperature for 1 hour. 0.78 ml (3.1 mmole) of a 4N solution of hydrogen chloride in dioxane were then added to the reaction mixture, after which the reaction mixture was extracted with methylene chloride. The organic extract was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was crystallized by the addition of diethyl ether, to afford 2.0 g of the dihydrate of the title compound, melting at 113 - 120 °C.

Elemental analysis:

Calculated for $C_{36}H_{47}N_5O_7S \cdot 2\,H_2O$:								
Found:	C,	59.23%;	H,	7.04%;	N,	9.60%;	S,	4.39%.
	C,	59.04%;	H,	7.03%;	N,	9.66%;	S,	4.52%.

24(c) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(1-ethyl-2-pyrrolidinylmethyl)amide

78 mg (0.43 mmole) of diethyl cyanophosphonate (95%) and 60 µl (0.43 mmole) of triethylamine were added to a solution of 250 mg (0.36 mmole) of N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin [prepared as described in step (b) above] and 69 mg (0.54 mmole) of 2-aminomethyl-1-ethylpyrrolidine in 5 ml of tetrahydrofuran, whilst ice-cooling, and the mixture was then agitated at room temperature for 5 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 5 : 1 by volume mixture of methylene chloride and methanol), to afford 120 mg of the dihydrate of the title compound, melting at 63 - 67°C.

Elemental analysis:

Calculated for $C_{43}H_{61}N_7O_6S \cdot 2\,H_2O$:								
Found:	C,	61.47%;	H,	7.80%;	N,	11.67%;	S,	3.82%.
	C,	61.22%;	H,	7.52%;	N,	11.48%;	S,	3.78%.

EXAMPLE 25

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(2-thienyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)-amide

25(a) N-[N-(t-Butoxycarbonyl)-3-(2-thienyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide

0.25 g (2.48 mmole) of triethylamine and 0.15 g (0.9 mmole) of diethyl cyanophosphonate (95%) were added, whilst ice-cooling, to a suspension of 0.3 g (0.74 mmole) of cyclostatin-(2-morpholinoethyl)amide dihydrochloride [prepared as described in Preparation 9(b)] and 0.2 g (0.74 mmole) of N-(t-butoxycarbonyl)-3-(2-thienyl)-DL-alanine in 10 ml of anhydrous tetrahydrofuran and the mixture was stirred for 0.5 hours and the stirring was continued at room temperature for a further 15 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of methylene chloride and methanol), to afford 0.31 g (72.1 %) of the title compound as an amorphous substance.

Elemental analysis:

Calculated for $C_{29}H_{48}N_4O_6S$:								
Found:	C,	59.97%;	H,	8.33%;	N,	9.65%;	S,	5.52%.
	C,	59.70%;	H,	8.18%;	N,	9.62%;	S,	5.68%.

25(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(2-thienyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 0.21 g (0.366 mmole) of N-[N-(t-butoxycarbonyl)-3-(2-thienyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in step (a) above] in 5 ml of methanol, and the mixture was stirred at room temperature for 2 hours. At the end of this time, the solvent was removed by distillation to dryness under reduced pressure, and the residue was suspended in anhydrous tetrahydrofuran. 0.13 g (0.366 mmole) of N-morpholinoacetyl-3-(1-naphthyl)-L-alanine (prepared by a procedure similar to that described in Preparation 17), 0.15 g (1.46 mmole) of triethylamine and 72 mg (0.44 mmole) of diethyl cyanophosphonate (95%) were then added, whilst ice-cooling, to the resulting suspension. The mixture was stirred for 0.5 hours at the temperature of ice-cooling, and then the stirring was continued at room temperature for a further 16 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of methylene chloride and methanol), to afford 0.24 g (77.4 %) of the trihydrate of the title compound as an amorphous substance.

Silica gel thin layer chromatography, Rf value 0.53.

Elemental analysis:

Calculated for $C_{43}H_{60}N_6O_7S \cdot 3H_2O$:								
	C,	60.12%;	H,	7.74%;	N,	9.78%;	S,	3.73%.
Found:	C,	59.62%;	H,	7.03%;	N,	9.98%;	S,	3.87%.

EXAMPLE 26

A compound outside the scope of the present invention.

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-[3-(2-methylpiperidino)propyl]amide

26(a) N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-[3-(2-methylpiperidino)propyl]amide

0.09 g (0.48 mmole) of diethyl cyanophosphonate (95%) and 0.05 g (0.48 mmole) of triethylamine were added, whilst ice-cooling, to a solution of 0.19 g (0.4 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin and 0.08 g (0.48 mmole) of N-(3-aminopropyl)-2-pipecoline in 5 ml of dimethylformamide, and the mixture was stirred at the temperature of ice-cooling for 1 hour and the stirring was continued at room temperature overnight. The reaction mixture was then extracted with twice its own volume of ethyl acetate, and the extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 3 : 1 by volume mixture of methylene chloride and methanol), to afford 0.23 g of the title compound as an amorphous substance.

26(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-[3-(2-methylpiperidino)propyl]amide

The t-butoxycarbonyl group was removed from 0.23 g (0.38 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-[3-(2-methylpiperidino)propyl]amide [prepared as described in step (a) above] by treating it with a 4N solution of hydrog n chlorid in dioxan . The hydrochlorid thus obtain d and 0.13 g (0.38 mmole) of N-m rpholinoacetyl-3-(1-naphthyl)-L-alanin were then dissolved in 5 ml of dimethylformamid , and 0.08 g (0.46 mmole) of di thyl cyanophosphonate (95%) and 0.17 g (1.71 mmol) of triethylamin were added, whilst ice-cooling, to th solution. The resulting mixtur was stirred, whilst ice-cooling, for 1 hour and then the stirring was continued at room temperatur overnight. The reaction mixture was th n extracted with twice its own volume of thyl acetate, th extract was washed with a 5% w/v aqueous solution of sodium bicarbonat and with a saturated aqueous solution of sodium chloride, in that

order, after which it was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 5 : 1 by volum mixture of methylene chloride and methanol), to afford 0.60 g of the 3.5-hydrat of the title compound, melting at 97 - 101°C.

Elemental analysis:

Calculated for $C_{45}H_{65}N_7O_6S \cdot 3.5\ H_2O$:								
Found:	C,	60.37%;	H,	8.11%;	N,	10.95%;	S,	3.58%.
	C,	60.65%;	H,	7.95%;	N,	10.69%;	S,	3.48%.

EXAMPLE 27

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

A procedure similar to that described in Example 26(a) was repeated, except that the N-(3-aminopropyl)-2-pipecoline was replaced by 70 mg (0.48 mmole) of 1-(3-aminopropyl)-2-pyrrolidinone and this was reacted with 190 mg (0.4 mmole) of N-[N-t-butoxycarbonyl)-3-(4-thiazolyl)-DL-alanyl]-cyclostatin [prepared by a procedure similar to that described in Example 24(b)], and then the product was subsequently treated as described in Example 25(b), to afford 240 mg of the dihydrate of the title compound as white crystals, melting at 95 - 98°C.

Elemental analysis:

Calculated for $C_{43}H_{59}N_7O_7S \cdot 2\ H_2O$:						
Found:	C,	60.46%;	H,	7.44%;	N,	11.48%.
	C,	60.70%;	H,	7.39%;	N,	11.51%.

EXAMPLE 28

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-L-histidyl}-cyclostatin-(2-morpholinoethyl)amide

28(a) N-[N-(t-Butoxycarbonyl)-N^{im}-p-toluenesulphonyl-L-histidyl]-cyclostatin-(2-morpholinoethyl)amide

0.28 g (1.52 mmole) of diethyl cyanophosphonate (95%) and 0.34 g (3.31 mmole) of triethylamine were added, whilst ice-cooling, to a solution of 0.57 g (1.38 mmole) of N-(t-butoxycarbonyl)-N^{im}-p-toluenesulphonyl-L-histidine and 0.50 g (1.38 mmole) of cyclostatin-(2-morpholinoethyl)amide in 10 ml of dimethylformamide, and the mixture was stirred, whilst ice-cooling, for 1 hour; the stirring was then continued at room temperature overnight. At the end of this time, the reaction mixture was extracted with ethyl acetate, the extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous sodium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 15 : 1 by volume mixture of methylene chloride and methanol), to afford 0.56 g of the title compound as an amorphous substance.

28(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-N^{im}-p-tolu nesulphonyl-L-histidyl}-cyclostatin-(2-morpholinoethyl)amide

The t-butoxycarbonyl group was r moved from 0.56 g (0.78 mmole) of N-[N-(t-butoxycarbonyl)-N^{im}-p-toluenesulphonyl-L-histidyl]-cyclostatin-(2-morpholinoethyl)amide [prepared as described in step (a) above]

by treating it with a 4N solution of hydrogen chloride in dioxane. The hydrochloride thus obtained and 0.27 g (0.78 mmole) of N-morpholinoacetyl-3-(1-naphthyl)-L-alanine were dissolved in 5 ml of dimethylformamid . 0.39 g (2.15 mmole) of di thyl cyanophosphonate (95%) and 0.39 g (3.86 mmole) of triethylamine were added, whilst ice-cooling, to the solution, and then the mixture was stirred, whilst ice-cooling, for 1 hour; the stirring was then continued at room temperature for a further 4 days. At the end of this time, the reaction mixture was extracted with twice its own volume of ethyl acetate, and the extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous sodium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel thin layer chromatography (developing solvent: a 10 : 1 by volume mixture of methylene chloride and methanol), to afford 0.12 g of the title compound as an amorphous substance.

28(c) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-L-histidyl}-cyclostatin-(2-morpholinoethyl)amide

0.07 g (0.52 mmole) of 1-hydroxybenzotriazole was added to a solution of 0.12 g (0.13 mmole) of N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-N^{im}-p-toluenesulphonyl-L-histidyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in step (b) above] in 3 ml of methanol, and the mixture was stirred at room temperature for 4 hours. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and was then extracted with ethyl acetate. The extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was crystallized by the addition of diethyl ether, to afford 0.90 g of the trihydrate of the title compound, melting at 103 - 106°C.

Elemental analysis:

Calculated for $C_{42}H_{60}N_8O_7 \cdot 3\,H_2O$:						
	C,	59.84%;	H,	7.89%;	N,	13.29%.
Found:	C,	60.10%;	H,	7.98%;	N,	13.46%.

EXAMPLE 29

N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 21(b), 175 mg (0.5 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in Example 21(a)] and 74.6 mg (0.5 mmole) of N-benzyl-N-isopropylamine were reacted together and subsequently treated as described in Example 21(c), to afford 175 mg of the dihydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.51.

Elemental analysis:

Calculated for $C_{48}H_{65}N_7O_6S \cdot 2\,H_2O$:								
	C,	63.76%;	H,	7.69%;	N,	10.84%;	S,	3.55%.
Found:	C,	63.75%;	H,	7.50%;	N,	10.59%;	S,	3.84%.

EXAMPLE 30

N-[N-{N-[4-(4-Chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide

Following a procedure similar to that described in Example 21(b), 175 mg (0.5 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in Example 21(a)] and 143 mg (0.5 mmole) of 1-(4-chlorobenzhydryl)piperazine were reacted together and subsequently treated as described in Example 21(c), to afford 168 mg of the monohydrate of the title compound as white crystals, melting at 75 - 80°C.

Elemental analysis:

Calculated for $C_{55}H_{69}ClN_8O_6S \cdot H_2O$:						
Found:	C,	61.75%;	H,	7.01%;	N,	12.00%.
	C,	61.66%;	H,	6.89%;	N,	11.86%.

EXAMPLE 31

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-(2-morpholinoethyl)-amide

2 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 200 mg (0.370 mmole) of N-(t-butoxycarbonyl)-L-leucyl-cyclostatin-(2-morpholinoethyl)amide in 2 ml of methanol, and the mixture was stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by distillation to dryness under reduced pressure, and the residue was dissolved in 5 ml of dimethylformamide. 140 mg (0.372 mmole) of N-(N-methyl-N-benzylaminoacetyl)-3-(1-naphthyl)-L-alanine, 0.26 ml (1.87 mmole) of triethylamine and 76 mg (0.443 mmole) of diethyl cyanophosphonate (95%) were then added to the resulting solution, and the reaction mixture was stirred at room temperature for 4 hours, after which it was allowed to stand overnight. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of methylene chloride and methanol), to afford 202 mg of the monohydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.51.

Elemental analysis:

Calculated for $C_{46}H_{66}N_6O_6 \cdot H_2O$:						
Found:	C,	67.62%;	H,	8.39%;	N,	10.29%.
	C,	67.43%;	H,	8.19%;	N,	10.26%.

EXAMPLE 32

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-(2-morpholinoethyl)amide

A procedure similar to that described in Example 31 was repeated, but using 138 mg (0.375 mmole) of N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanin (prepar d by a procedure similar to that described in Preparation 19) instead of the N-(N-methyl-N-benzylaminoac tyl)-3-(1-naphthyl)-L-alanine, and this was reacted with 200 mg (0.370 mmole) of N-(t-butoxycarbonyl)-L-leucyl-cyclostatin-(2-morpholinoethyl)amide [prepared by a procedure similar to that described in Example 2(a)], to give 106 mg of the p ntahydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.50.

Elemental analysis:

Calculated for $C_{45}H_{70}N_6O_6 \cdot 5\ H_2O$:						
	C,	61.34%;	H,	9.15%;	N,	9.54%.
Found:	C,	61.33%;	H,	9.00%;	N,	9.43%.

EXAMPLE 33

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

5 ml of a 4N solution of hydrogen chloride in dioxane were added to a solution of 300 mg (0.54 mmole) of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide (prepared as described in Preparation 18) in 5 ml of methanol, and the mixture was stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by distillation to dryness under reduced pressure, and the residue was dissolved in 10 ml of dimethylformamide. 199 mg (0.54 mmole) of N-(N-methyl-N-cyclohexylaminoacetyl)-3-(1-naphthyl)-L-alanine, 249 mg (2.46 mmole) of triethylamine and 150 mg (0.92 mmole) of diethyl cyanophosphonate (95%) were then added to the resulting solution, and the mixture was stirred at room temperature for 4 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 360 mg of the hemihydrate of the title compound as white crystals, melting at 75 - 82 °C.

Elemental analysis:

Calculated for $C_{46}H_{70}N_6O_6 \cdot {}^1/_2\ H_2O$:						
	C,	68.03%;	H,	8.81%;	N,	10.35%.
Found:	C,	67.86%;	H,	8.63%;	N,	10.14%.

EXAMPLE 34

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

A procedure similar to that described in Example 33 was repeated, except that 203 mg (0.54 mmole) of N-(N-benzyl-N-methylaminoacetyl)-(1-naphthyl)-L-alanine (prepared by a procedure similar to that described in Preparation 19) were used instead of the N-(N-methyl-N-cyclohexylaminoacetyl)-3-(1-naphthyl)-L-alanine, and this was reacted with 300 mg (0.54 mmole) of N-[N-(t-butoxycarbonyl-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide (prepared by a procedure similar to that described in Preparation 18), to give 350 mg of the monohydrate of the title compound as white crystals, melting at 78 - 86 °C.

Elemental analysis:

Calculated for $C_{47}H_{66}N_6O_6 \cdot H_2O$:						
	C,	68.09%;	H,	8.27%;	N,	10.14%.
Found:	C,	68.40%;	H,	8.22%;	N,	10.05%.

EXAMPLE 35

N-{N-[N-(N-Butyl-N-m thylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

A procedure similar to that described in Example 33 was repeated, except that 280 mg (0.70 mmole) of N-(N-butyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine (prepared by a procedure similar to that described in Preparation 19) were used instead of the N-(N-methyl-N-cyclohexylaminoacetyl)-3-(1-naphthyl)-L-alanine, and this was reacted with 300 mg (0.54 mmole) of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide, to give 270 mg of the 2.5-hydrate of the title compound as white crystals, melting at 66 - 70 °C.

Elemental analysis:

Calculated for $C_{44}H_{68}N_6O_6 \cdot 2.5\ H_2O$:						
Found:	C,	65.00%;	H,	8.93%;	N,	10.34%.
	C,	64.75%;	H,	8.81%;	N,	10.20%.

EXAMPLE 36

N-{N-[N-(N-Diisobutylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide

A procedure similar to that described in Example 27(c) was repeated, except that 140 mg (0.35 mmole) of methyl N-(N,N-diisobutylaminoacetyl)-3-(1-naphthyl)-L-alanate were employed instead of the methyl N-(N,N-diethylaminoacetyl)-3-(1-naphthyl)-L-alanate, and this was reacted with the compound which had been prepared by removing the t-butoxycarbonyl group from 208 mg (0.35 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide [prepared by a procedure similar to that described in Example 2(a)], to give 230 mg of the monohydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.49.

Elemental analysis:

Calculated for $C_{46}H_{69}N_7O_6S \cdot H_2O$:								
Found:	C,	63.79%;	H,	8.26%;	N,	11.32%;	S,	3.70%.
	C,	63.51%;	H,	8.29%;	N,	11.04%;	S,	3.58%.

EXAMPLE 37

N-[N-{N-[4-(4-Fluorophenyl)-1-piperazinyl]acetyl-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-DL-alanyl]-cyclostatin-(2-morpholinoethyl)amide

A procedure similar to that described in Example 16(b) was repeated, except that 200 mg (0.26 mmole) of N-{N-[N-(t-butoxycarbonyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide [prepared as described in Example 16(a)] and 63.1 mg (0.26 mmole) of [4-(4-fluorophenyl)-1-piperazinyl]acetic acid were reacted together to giv 51 mg of the dihydrate of th title compound as a white powder.

Silica g l thin lay r chromatography, Rf value 0.50.

Elemental analysis:

Calculated for $C_{48}H_{63}FN_8O_6S \cdot 2\,H_2O$:						
	C,	61.65%;	H,	7.22%;	N,	11.98%.
Found:	C,	61.88%;	H,	7.20%;	N,	11.70%.

EXAMPLE 38

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-histidyl-cyclostatin}-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

A procedure similar to that described in Example 34 was repeated, except that 150 mg (0.26 mmole) of N-[N-(t-butoxycarbonyl)-L-histidyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide were employed instead of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide, and this was reacted with 120 mg (0.31 mmole) of N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine, to give 118 mg of the sesquihydrate of the title compound as a white powder, melting at 91 - 94 °C.

Elemental analysis:

Calculated for $C_{47}H_{62}N_8O_6 \cdot 1.5\,H_2O$:						
	C,	65.48%;	H,	7.60%;	N,	13.00%.
Found:	C,	65.27%;	H,	7.31%;	N,	12.83%.

EXAMPLE 39

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-(2-morpholinoethyl)amide

2 ml of methanol and 2 ml of a 4N solution of hydrogen chloride in dioxane were added to 130 mg (0.24 mmole) of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-(2-morpholinoethyl)amide (prepared by a procedure similar to that described in Example 2(a)], and the mixture was stirred for 1 hour to remove the t-butoxycarbonyl group. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue, together with 82.2 mg (0.24 mmole) of N-morpholinoacetyl-3-(1-naphthyl)-L-alanine, was suspended in 15 ml of anhydrous tetrahydrofuran. 97 mg (0.96 mmole) of triethylamine and subsequently 79.3 mg of diphenylphosphoric azide were then added to the resulting suspension, whilst ice-cooling, and the mixture was stirred for 0.5 hours; the stirring was then continued at room temperature for a further 64 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (developing solvent: a 9 : 1 by volume mixture of methylene chloride and methanol), to afford 100 mg of the dihydrate of the title compound as a colourless amorphous substance.

Silica gel thin layer chromatography, Rf value 0.50.

Elemental analysis:

Calculat d for $C_{42}H_{64}N_6O_7 \cdot 2\,H_2O$:						
	C,	62.98%;	H,	8.56%;	N,	10.49%.
Found:	C,	62.98%;	H,	8.14%;	N,	10.36%.

EXAMPLE 40

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

A procedure similar to that described in Example 33 was repeated, except that 175 mg (0.53 mmole) of N-morpholinoacetyl-3-(1-naphthyl)-L-alanine were employed instead of the N-(N-methyl-N-cyclohexylaminoacetyl)-3-(1-naphtyl)-L-alanine, and this was reacted with 238 mg (0.43 mmole) of N-[N-(t-butoxycarbonyl)-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide, to give 109 mg of the monohydrate of the title compound as white crystals, melting at 105 - 109 °C.

Elemental analysis:

Calculated for $C_{43}H_{64}N_6O_7 \cdot H_2O$:						
Found:	C,	64.96%;	H,	8.37%;	N,	10.57%.
	C,	64.83%;	H,	8.21%;	N,	10.32%.

EXAMPLE 41

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]-amide

41(a) N-(t-Butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide

A procedure similar to that described in Example 20(a) was repeated, except that 0.33 g (3.81 mmole) of (S)-2-methylbutylamine was employed instead of the 2-morpholinoethylamine, and this was reacted with 1.00 g (3.17 mmole) of N-(t-butoxycarbonyl)cyclostatin, to give 1.13 g (93%) of the title compound as a white powder.

41(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide

A procedure similar to that described in Example 16(a) was repeated, except that 0.50 g (1.30 mmole) of N-(t-butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide were employed instead of the N-(t-butoxycarbonyl)-cyclostatin-(2-morpholinoethyl)amide, and this was reacted with the compound which had been prepared by removing the t-butoxycarbonyl group from 354 mg (1.30 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine; subsequent reactions were carried out as described in Example 16(b), to give 254 mg (72%) of the 2.5-hydrate of the title compound as a white powder.

Silica gel thin layer chromatography, Rf value 0.63.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_6S \cdot 2.5\ H_2O$:								
Found:	C,	60.94%;	H,	7.60%;	N,	10.40%;	S,	3.97%.
	C,	60.56%;	H,	7.14%;	N,	10.61%;	S,	3.99%.

EXAMPLE 42

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-propylamide

42(a) N-(t-Butoxycarbonyl)-cyclostatin-propylamide

510 mg (1.6 mmoles) of N-(t-butoxycarbonyl)-cyclostatin, 90 mg (1.6 mmoles) of propylamine and 320 mg (3.2 mmoles) of triethylamine were added to 20 ml of anhydrous tetrahydrofuran. 280 mg (1.6 mmoles) of 95% diethyl cyanophosphonate (95%) were then added dropwise to the mixture, whilst ice-cooling, and the mixture was stirred for 4 hours at the temperature of ice-cooling, and then allowed to stand overnight. The reaction mixture was then concentrated by evaporation under reduced pressure, and the residue was diluted with water and then extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was triturated with a mixture of ethyl acetate and hexane to induce crystallization. 446 mg of the title compound, melting at 135 - 136 °C, were obtained.

42 (b)N-[N-(t-Butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-propylamide

440 mg (1.24 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-propylamide [prepared as described in step (a) above] and 8 ml of a 4N solution of hydrogen chloride in dioxane were added to 2 ml of methanol, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in 17 ml of anhydrous tetrahydrofuran. 340 mg (1.24 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine and 510 mg (5.0 mmoles) of triethylamine were added to the resulting solution, after which 210 mg (1.24 mmoles) of diethyl cyanophosphonate (95%) were added dropwise, whilst ice-cooling. The reaction mixture was then stirred for 4 hours, after which it was allowed to stand overnight. It was then concentrated by evaporation under reduced pressure. The residue was mixed with a small amount of water and then extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was triturated with a mixture of methylene chloride and hexane to induce crystallization. 513 mg of the title compound, melting at 198 - 200 °C, were obtained.

42(c) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-propylamide

510 mg (1.0 mmole) of N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-propylamide and 12 ml of a 4N solution of hydrogen chloride in dioxane were added to 4 ml of methanol, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in 20 ml of anhydrous tetrahydrofuran. 340 mg (1.0 mmole) of N-morpholino- acetyl-3-(1-naphthyl)-L-alanine and 510 mg (5.0 mmoles) of triethylamine were added to the resulting solution, after which 170 mg (1.0 mmole) of 95% diethyl cyanophosphonate (95%) were added dropwise, whilst ice-cooling, to the mixture. The reaction mixture was stirred for 4 hours at room temperature, allowed to stand overnight and then evaporated to dryness under reduced pressure. The residue was mixed with a small amount of water, and the resulting mixture was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was triturated with a mixture of methylene chloride and hexane to induce crystallization. 630 mg of the monohydrate of the title compound, melting at 189 - 191 °C, were obtained.

Elemental analysis:

Calculated for $C_{39}H_{54}N_6O_6S \cdot H_2O$:								
Found:	C,	62.21%;	H,	7.50%;	N,	11.16%;	S,	4.26%.
	C,	62.34%;	H,	7.32%;	N,	11.05%;	S,	3.99%.

EXAMPLE 43

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-butylamide

43(a) N-(t-Butoxycarbonyl)-cyclostatin-butylamide

Following a procedure similar to that described in Example 42(a), but reacting 510 mg (1.6 mmoles) of N-(t-butoxycarbonyl)-cyclostatine with 120 mg (1.6 mmoles) of butylamine (instead of the propylamine), 396 mg of the title compound were obtained as white crystals.

43(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-butylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 390 mg (1.05 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-butylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 290 mg (1.05 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 590 mg of the hemihydrate of the title compound were obtained as crystals, melting at 180 - 182 °C.

Elemental analysis:

Calculated for $C_{40}H_{56}N_6O_6S \cdot \frac{1}{2}H_2O$:								
	C,	63.38%;	H,	7.58%;	N,	11.09%;	S,	4.23%.
Found:	C,	63.09%;	H,	7.57%;	N,	10.97%;	S,	4.16%.

EXAMPLE 44

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-isobutylamide

44(a) N-(t-Butoxycarbonyl)-cyclostatin-isobutylamide

Following a procedure similar to that described in Example 42(a), but reacting 140 mg (1.9 mmoles) of isobutylamine (instead of the propylamine) and 500 mg (1.59 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 470 mg of the title compound were obtained as white crystals.

44(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-isobutylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 460 mg (1.24 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-isobutylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 340 mg (1.24 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 785 mg of the monohydrate of the title compound were obtained as crystals, melting at 195 - 197 °C.

Elemental analysis:

Calculated for $C_{40}H_{56}N_6O_6S \cdot H_2O$:								
	C,	62.64%;	H,	7.62%;	N,	10.96%;	S,	4.18%.
Found:	C,	62.94%;	H,	7.64%;	N,	10.85%;	S,	4.24%.

EXAMPLE 45

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-diisobutylamide

45(a) N-(t-Butoxycarbonyl)-cyclostatin-diisobutylamide

Following a procedure similar to that described in Example 42(a), but reacting 205 mg (1.59 mmoles) of diisobutylamine (instead of the propylamine) and 500 mg (1.59 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 560 mg of the title compound were obtained as a white powder.

45(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-diisobutylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 427 mg (1.0 mmole) of N-(t-butoxycarbonyl)-cyclostatin-diisobutylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 272 mg (1.0 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 690 mg of the title compound were obtained as an amorphous monohydrate.

Silica gel thin layer chromatography, Rf value 0.53, (developing solvent: a 30 : 1.5 by volume mixture of ethyl acetate and methanol).

Elemental analysis:

Calculated for $C_{44}H_{64}N_6O_6S \cdot H_2O$:								
	C,	64.21%;	H,	8.08%;	N,	10.21%;	S,	3.89%.
Found:	C,	64.51%;	H,	7.79%;	N,	10.47%;	S,	3.88%.

EXAMPLE 46

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-pentylamide

46(a) N-(t-Butoxycarbonyl)-cyclostatin-pentylamide

Following a procedure similar to that described in Example 42(a), but reacting 0.22 ml (1.9 mmoles) of pentylamine (instead of propylamine) and 500 mg (1.59 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 580 mg of the title compound were obtained as white crystals.

46(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-pentylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 580 mg (1.5 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-pentylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 463 mg (1.7 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 574 mg of the mono-hydrate of the title compound were obtained, melting at 141 - 143°C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_6S \cdot H_2O$:								
	C,	63.05%;	H,	7.74%;	N,	10.76%;	S,	4.10%.
Found:	C,	63.13%;	H,	7.63%;	N,	10.86%;	S,	4.05%.

EXAMPLE 47

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-isopentylamide

47(a) N-(t-Butoxycarbonyl)-cyclostatin-isopentylamide

Following a procedure similar to that described in Example 42(a), but reacting 0.22 ml (1.9 mmoles) of isopentylamine (instead of propylamine) and 500 mg (1.59 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 600 mg of the title compound were obtained as white crystals.

47(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-isopentylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 600 mg (1.56 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-isopentylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 425 mg (1.56 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 828 mg of the monohydrate of the title compound were obtained, melting at 160 - 162 °C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_6S \cdot H_2O$:								
Found:	C,	63.05%;	H,	7.74%;	N,	10.76%;	S,	4.10%.
	C,	63.26%;	H,	7.62%;	N,	10.74%;	S,	4.25%.

EXAMPLE 48

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(RS)-2-methylbutyl]-amide

48(a) N-(t-butoxycarbonyl)-cyclostatin-[(RS)-2-methylbutyl]amide

Following a procedure similar to that described in Example 42(a), but reacting 170 mg (1.9 mmoles) of (RS)-2-methylbutylamine (instead of the propylamine) and 500 mg (1.59 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 440 mg of the title compound were obtained as white crystals.

48(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(RS)-2-methyl-butyl]amide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 550 mg (1.43 mmoles) of N-(t-butoxycarbonyl)-[(RS)-2-methylbutyl]amide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 390 mg (1.43 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 862.5 mg of the hemihydrate of the title compound were obtained, melting at 138 - 140 °C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_6S \cdot {}^1/_2\ H_2O$:								
Found:	C,	63.79%;	H,	7.70%;	N,	10.88%;	S,	4.15%.
	C,	63.54%;	H,	7.67%;	N,	10.94%;	S,	4.17%.

EXAMPLE 49

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamide

49(a) N-(t-Butoxycarbonyl)-cyclostatin-hexylamide

Following a procedure similar to that described in Example 42(a), but reacting 380 mg (3.8 mmoles) of hexylamine (instead of the propylamine) and 1.0 g (3.17 mmoles) of N-(t-butoxycarbonyl)-cyclostatine, 1.1 g of the title compound were obtained.

49(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamide

Following a procedure similar to that described in Example 42(b), followed by a procedure similar to that described in Example 42(c), but reacting 1.1 g (2.76 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-hexylamide [prepared as described in step (a) above, instead of the N-(t-butoxycarbonyl)-cyclostatin-propylamide] and 750 mg (2.76 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, 1.40 g of the monohydrate of the title compound were obtained, melting at 154 - 156 °C.

Elemental analysis:

Calculated for $C_{42}H_{60}N_6O_6S \cdot H_2O$:								
	C,	63.45%;	H,	7.86%;	N,	10.57%;	S,	4.03%.
Found:	C,	63.67%;	H,	7.85%;	N,	10.60%;	S,	4.09%.

The monohydrate thus obtained was recrystallised from methylene chloride, to give the title compound, melting at 180 - 182 °C.

Elemental analysis:

Calculated for $C_{42}H_{60}N_6O_6S$:								
	C,	64.92%;	H,	7.78%;	N,	10.82%;	S,	4.13%.
Found:	C,	65.02%;	H,	7.91%;	N,	10.64%;	S,	3.97%.

EXAMPLE 50

N-{N-[N-(Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-isopentylamide

539 mg (1.0 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-cyclostatin-isopentylamide [prepared by a procedure similar to that described in Example 47(a)] and 12 ml of a 4N solution of hydrogen chloride in dioxane were added to 4 ml of methanol, and the mixture was stirred at room temperature for 1 hour. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 20 ml of anhydrous tetrahydrofuran. 376 mg (1.0 mmole) of N-(benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 19) and 510 mg (5.0 mmoles) of triethylamine were then added to the solution, after which 170 mg (1.0 mmole) of diethyl cyanophosphonate (95%) w re added dropwis to the mixture, whilst ice-cooling. Th mixture was then stirred for 16 hours. At the end of this tim , the reaction mixture was vaporated to dryness under reduced pressure. The r sidue was mixed with a small amount of water and then extract d with ethyl acetate. The organic extract was washed with water, dried ov r anhydrous magnesium sulphate and concentrated by vaporation under reduced pressur . The residu was triturated with a mixtur of methylene chlorid and hexane to crystallize it. 670 mg of the hemihydrat of the title compound were obtained, melting at 128 - 132 °C.

Elemental analysis:

Calculated for $C_{45}H_{60}N_6O_5S \cdot {}^1/_2H_2O$:								
	C,	67.05%;	H,	7.63%;	N,	10.43%;	S,	3.98%.
Found:	C,	67.00%;	H,	7.55%;	N,	10.43%;	S,	3.71%.

EXAMPLE 51

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-butylamide

520 mg (1.0 mmole) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-cyclostatin-butylamide [prepared by a procedure similar to that described in Example 43(a)] and 12 ml of a 4N solution of hydrogen chloride in dioxane were added to 4 ml of methanol, and the mixture was stirred for 1 hour at room temperature. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 20 ml of anhydrous tetrahydrofuran. 370 mg (1.0 mmole) of N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 20) and 510 mg (5.0 mmoles) of triethylamine were then added to the resulting solution, after which 170 mg (1.0 mmole) of 95% diethyl cyanophosphonate were added dropwise to the mixture, whilst ice-cooling. The mixture was then stirred at room temperature for 17 hours. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure. The residue was mixed with a small amount of water, and the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness under reduced pressure. The residue was triturated with isopropyl ether to crystallize it. 480 mg of the hemihydrate of the title compound were obtained, melting at 78 °C.

Elemental analysis:

Calculated for $C_{43}H_{62}N_6O_5S \cdot {}^1/_2H_2O$:								
	C,	65.87%;	H,	8.10%;	N,	10.72%;	S,	4.09%.
Found:	C,	65.82%;	H,	8.16%;	N,	10.55%;	S,	4.02%.

EXAMPLE 52

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamide

Following a procedure similar to that described in Example 51, but using 400 mg (0.724 mmoles) of N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-cyclostatin-hexylamide [prepared by a procedure similar to that described in Example 49(a)] and 270 mg (0.724 mmoles) of N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 20), 380 mg of the hemihydrate of the title compound were obtained, melting at 117 - 119 °C.

Elemental analysis:

Calculated for $C_{45}H_{66}N_6O_5S \cdot {}^1/_2H_2O$:								
	C,	66.55%;	H,	8.32%;	N,	10.35%;	S,	3.95%.
Found:	C,	66.55%;	H,	8.31%;	N,	10.49%;	S,	4.11%.

EXAMPLE 53

N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]-amide

53(a) N-[N-(t-Butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-[(S)-2-methylbutyl]amide

Following a procedure similar to that described in Example 41(b), but reacting 330 mg (1.3 mmoles) of N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanine [prepared as described in Preparation 8, instead of the N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine] and 500 mg (1.3 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-[(S)-2-methylbutyl]amide [prepared as described in Example 10(a)], 520 mg of the title compound were obtained.

53(b) N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide

Following a procedure similar to that described in Example 41(b), but reacting 200 mg (0.38 mmoles) of N-[N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl]-cyclostatin-[(S)-2-methylbutyl]amide {prepared as described in step (a) above, instead of the N-[N-(t-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl]-cyclostatin-[(S)-2-methylamide]} and 130 mg (0.38 mmoles) of N-morpholinoacetyl-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 17), 260 mg of the dihydrate of the title compound were obtained, melting at 124 - 126 °C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_7 \cdot 2H_2O$:						
	C,	62.89%;	H,	7.98%;	N,	10.73%.
Found:	C,	62.63%;	H,	7.76%;	N,	10.50%.

EXAMPLE 54

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide

Following a procedure similar to that described in Example 53, but reacting 120 mg (0.38 mmoles) of N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine [prepared as described in Preparation 19, instead of the N-morpholinoacetyl-3-(1-naphthyl)-L-alanine] and 200 mg (0.38 mmoles) of N-(t-butoxycarbonyl)-3-(5-isoxazolyl)-L-alanyl-cyclostatin-[(S)-2-methylbutyl]amide [prepared as described in Example 53-(a)], 220 mg of the sesquihydrate of the title compound were obtained, melting at 138 - 140 °C.

Elemental analysis:

Calculated for $C_{41}H_{58}N_6O_6 \cdot {}^3/_2H_2O$:						
	C,	64.97%;	H,	8.11%;	N,	11.09%.
Found:	C,	64.83%;	H,	7.98%;	N,	10.71%.

EXAMPLE 55

N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-histidyl}-cyclostatin-[(RS)-2-methylbutyl]amide

55(a) N-[N-(t-butoxycarbonyl)-L-histidyl]-cyclostatin-[(RS)-2-methylbutyl]amide

2.5 g (6.5 mmoles) of N-(t-butoxycarbonyl)-cyclostatin-[(RS)-2-methylbutyl]amide [prepared as described in Example 10(a)] were dissolved in 30 ml of a 4N solution of hydrogen chloride in dioxane, and then the solution was stirred for 1 hour at room temperature. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 20 ml of dimethylformamide, and then 3.29 g (32.5 mmoles) of triethylamine and 2.16 g (8.45 mmoles) of N-(t-butoxycarbonyl)-L-histidine were added to the resulting solution. 1.45 g (8.45 mmoles) of diethyl cyanophosphonate (95%) were then added dropwise to the solution, which was then stirred for 18 hours, whilst ice-cooling. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was mixed with a small amount of water and then extracted with ethyl acetate. The organic extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous sodium sulphate, after which the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel thin-layer chromatography (developing solvent: a 10 : 1 by volume mixture of methylene chloride and methanol), to afford 2.03 g of the title compound.

55(b) N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-histidyl}-cyclostatin-[(RS)-2-methylbutyl]amide

0.52 g (1.0 mmole) of N-[N-(t-butoxycarbonyl)-L-histidyl]-cyclostatin-[(RS)-2-methylbutyl]amide [prepared as described in step (a) above] was dissolved in 7.5 ml of a 4N solution of hydrogen chloride in dioxane and stirred for 1 hour. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of dimethylformamide, and then 0.51 g (5.0 mmoles) of triethylamine and 0.45 g (1.2 mmoles) of N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine (prepared as described in Preparation 19) were added to the resulting solution. 0.21 g (1.2 mmoles) of diethyl cyanophosphonate (95%) were then added dropwise to the mixture, after which it was stirred for 17 hours, whilst ice-cooling. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was mixed with a small amount of water and then extracted with ethyl acetate. The organic extract was washed with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous sodium sulphate, after which the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel thin-layer chromatography (developing solvent: a 10 : 1 by volume mixture of methylene chloride and methanol), to afford 0.54 g of the sesquihydrate of the title compound, melting at 103 - 106°C.

Elemental analysis:

Calculated for $C_{45}H_{61}N_7O_5 \cdot {}^3/_2H_2O$:						
Found:	C,	66.97%;	H,	7.99%;	N,	12.15%.
	C,	66.93%;	H,	7.70%;	N,	12.09%.

EXAMPLE 56

N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-histidyl}-cyclostatin-[(RS)-2-methylbutyl]amide

Following a procedure similar to that described in Example 55(b), but reacting 0.66 g (1.8 mmoles) of N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine [prepared as described in Preparation 20], instead of the N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine and 0.78 g (1.5 mmoles) of N-[N-

(t-butoxycarbonyl)-L-histidyl]-cyclostatin-[(RS)-2-methylbutyl]amide, 0.62 g of the dihydrate of the title compound was obtained, melting at 110 - 113 °C.

Elemental analysis:

Calculated for $C_{44}H_{65}N_7O_5 \cdot 2H_2O$:						
	C,	65.40%;	H,	8.61%;	N,	12.13%.
Found:	C,	65.44%;	H,	8.31%;	N,	12.10%.

PREPARATION 1

N-[3-(1-Naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone

14.8 mmole of butyllithium in hexane were added dropwise to a solution of 2.63 g (14.8 mmole) of (S)-(-)-4-benzyl-2-oxazolidinone dissolved in 50 ml of anhydrous tetrahydrofuran at -78 °C under an atmosphere of nitrogen. The mixture was stirred for 30 minutes at this temperature, and then 2.95 g (13.5 mmole) of 1-naphthylpropionyl chloride in 15 ml of anhydrous tetrahydrofuran were slowly added dropwise at the same temperature; the mixture was then stirred for 3 hours. At the end of this time, a saturated aqueous solution of sodium chloride was added to the mixture, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, and then freed from the solvent by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 1 : 4 by volume mixture of ethyl acetate and hexane), to afford 4.65 g (96%) of the title compound as a white amorphous substance.
Mass Spectrum m/e: 359 (M^+).

PREPARATION 2

N-[(2-Benzyloxycarbonyl)methyl-3-(1-naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone

15.6 mmole of butyllithium in hexane were added dropwise to a solution of 2.18 ml (15.6 mmole) of diisopropylamine dissolved in 40 ml of anhydrous tetrahydrofuran at -78 °C under an atmosphere of nitrogen, and then the mixture was stirred for 15 minutes at the same temperature. A solution of 4.65 g (12.9 mmole) of N-[3-(1-naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone (prepared as described in Preparation 1) dissolved in 15 ml of anhydrous tetrahydrofuran was then slowly added dropwise to the above mixture at the same temperature, and the mixture was stirred for 30 minutes. At the end of this time, 6.13 ml (38.7 mmole) of benzyl bromoacetate were added to the mixture, which was then stirred for 6 hours at the same temperature. At the end of this time, 15.6 ml of 1N aqueous hydrochloric acid and 100 ml of a saturated aqueous solution of sodium chloride were added to the mixture. The mixture was then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was purified by medium pressure silica gel column chromatography (eluent: a 1 : 6 by volume mixture of ethyl acetate and hexane), to afford 3.23 g (49%) of the title compound as a colourless oil.
Mass Spectrum m/e: 507 (M^+).

Elemental analysis:

Calculat d for $C_{32}H_{29}NO_5$:						
	C,	75.72%;	H,	5.76%;	N,	2.76%.
Found:	C,	75.34%;	H,	5.90%;	N,	2.76%.

PREPARATION 3

N-[2-(Morpholinocarbonyl)methyl-3-(1-naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone

A solution of 1.60 g (3.15 mmole) of N-[(2-benzyloxycarbonyl)methyl-3-(1-naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone (prepared as described in Preparation 2) dissolved in 100 ml of ethanol was stirred in an atmosphere of hydrogen and in the presence of 200 mg of a 10% w/w palladium-on-carbon catalyst at room temperature for 3 hours. At the end of this time, the catalyst was removed by filtration, and the filtrate was concentrated by evaporation under reduced pressure, to afford 1.30 g (99%) of the corresponding free carboxylic acid, which was dissolved in 20 ml of anhydrous tetrahydrofuran. 0.33 ml (3.78 mmole) of morpholine was added to the solution, after which 0.57 ml (3.76 mmole) of diethyl cyanophosphonate (95%) and 0.52 ml of triethylamine were added, whilst ice-cooling, under an atmosphere of nitrogen. The mixture was stirred at the same temperature for 3 hours, after which it was freed from the solvent by evaporation under reduced pressure. The residue was purified by medium pressure column chromatography through silica gel (eluent: a 2 : 1 by volume mixture of ethyl acetate and hexane), to afford 1.23 g (81%) of the title compound as white crystals, melting at 80 - 82 °C.

Mass Spectrum m/e: 486 (M^+)

$[\alpha]_D^{25}$ = +107.9 (c = 0.42, methanol).

Elemental analysis:

Calculated for $C_{29}H_{30}N_2O_5$:						
Found:	C,	71.59%;	H,	6.21%;	N,	5.76%.
	C,	70.07%;	H,	6.12%;	N,	5.71%.

PREPARATION 4

(2R)-3-(Morpholinocarbonyl)-2-(1-naphthylmethyl)propionic acid

221 mg (5.27 mmole) of lithium hydroxide monohydrate were added, whilst ice-cooling, to a solution of 1.28 g (2.63 mmole) of N-[2-(morpholinocarbonyl)methyl-3-(1-naphthyl)propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone (prepared as described in Preparation 3) dissolved in a mixture of 40 ml of tetrahydrofuran and 10 ml of water. The mixture was stirred at the same temperature for 3 hours, after which it was freed from the solvent by evaporation under reduced pressure. A 10% w/v aqueous solution of sodium hydroxide was added to the residue, and the mixture was extracted with methylene chloride. The aqueous layer was separated, adjusted with hydrochloric acid to a pH value of 2 and then extracted with methylene chloride. The extract was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure, to afford 750 mg (87%) of the title compound as white crystals, melting at 62 - 66 °C.

Mass Spectrum m/e: 328 (M^+ + 1).

$[\alpha]_D^{25}$ = +5.0° (c = 0.18, methanol).

PREPARATION 5

Diethyl 5-isoxazolylmethylacetamidomalonate

3.1 g (70.7 mmole) of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to a solution of 14.0 g (6.43 mmole) of diethyl acetamidomalonate dissolved in 150 ml of dimethylformamide, whilst ice-cooling, and the mixtur was stirred for 1 hour. At th end of this tim , 23.9 g (0.148 mmol) of 5-bromomethylisoxazol wer added to th r action mixture, which was then stirred at room t mperatur for 4.5 hours. The r action mixture was then conc ntrat d by vaporation under reduced pr ssur , and th r sidue was mixed with water and extracted with ethyl acetate. Th xtract was washed with wat r and dried over anhydrous magnesium sulphate, after which it was concentrated by evaporation under reduc d pressure. The residue was purified by silica gel column chromatography (eluent: a 1 : 2 by volume mixture of thyl ac tate and hexane), to afford 14.78 g (77.1%) of the title compound, melting at 75 - 76 °C.

PREPARATION 6

3-(5-Isoxazolyl)-DL-alanine hydrochloride

120 ml of 6N aqueous hydrochloric acid were added to a suspension of 19.0 g (63.7 mmole) of diethyl 5-isoxazolylmethylacetamidomalonate (prepared as described in Preparation 5) in 40 ml of ethanol, and the mixture was heated under reflux and with stirring for 13 hours. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was triturated with acetone to afford crystals, which were collected by filtration. These crystals were washed with acetone and dried, to give 12.45 g (100%) of the title compound.

Elemental analysis:

Calculated for $C_6H_8N_2O_3$. HCl:								
Found:	C,	37.42%;	H,	4.71%;	N,	14.55%;	Cl,	18.41%.
	C,	37.54%;	H,	4.68%;	N,	14.43%;	Cl,	18.37%.

PREPARATION 7

N-Acetyl-3-(5-isoxazolyl)-DL-alanine

20 ml of pyridine and 20 ml of acetic anhydride were added to a solution of 12.45 g of 3-(5-isoxazolyl)-DL-alanine hydrochloride (prepared as described in Preparation 6) dissolved in 100 ml of methanol, whilst ice-cooling. The mixture was then stirred at room temperature for 8 hours, after which it was allowing to stand overnight. The mixture was then freed from the solvent by evaporation under reduced pressure. The residue was mixed with water and then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure, to afford 10.39 g (82.3%) of the title compound as a brown oil.

PREPARATION 8

N-(t-Butyroxycarbonyl)-(5-isoxazolyl)-L-alanine

A solution of 10.39 g (52.4 mmole) of N-acetyl-3-(5-isoxazolyl)-DL-alanine dissolved in 100 ml of water was adjusted to a pH value of 7.5 by adding a 2N aqueous solution of sodium hydroxide. 2.0 g of acylase were added to the resulting solution, and the mixture was stirred at 38°C for 24 hours. At the end of this time, the reaction mixture was filtered and the filtrate was adjusted to a pH value of 1 by adding concentrated hydrochloric acid. The mixture was agitated with ethyl acetate, and the aqueous layer was separated and adjusted to a pH value of 10 by adding potassium carbonate. 20 g of di(t-butoxy)dicarbonate, 40 ml of acetone and 100 ml of methanol were added to the solution, and the mixture was stirred at room temperature for 2.5 hours. It was then allowed to stand overnight, after which it was concentrated by evaporation under reduced pressure. 100 ml of water were added to the residue, and the mixture was adjusted to a pH value of 2.0 by adding citric acid. The reaction mixture was then extracted with ethyl acetate, and the extract was dried over anhydrous magnesium sulphate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography (eluent: a 95 : 5 by volume mixture of chloroform and methanol), to afford 2.99 g (22.3%) of the title compound as an oil.

PREPARATION 9

Cyclostatin-(2-morpholinoethyl)amide dihydrochlorid

9(a) N-(t-Butoxycarbonyl)-cyclostatin-(2-morpholinoethyl)amide

3.16 g of N-t-butoxycarbonylcyclostatine, 1.43 g of 2-morpholinoethylamin and 2.1 ml of triethylamine were added to 30 ml of anhydrous tetrahydrofuran. 2 g of diethyl cyanophosphonate (90%) were add d

dropwise to the mixture, whilst ice-cooling. The mixture was stirred for 4 hours, after which it was allowed to stand overnight. The reaction mixture was then concentrated by vaporation under reduced pressure, after which water was added, and the mixtur was extract d with ethyl acetat . The organic lay r was washed with a saturated aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride. It was then dried over anhydrous magnesium sulphate, and the solvent was removed by vaporation under reduced pressure. The residue was purified by column chromatography through silica gel (eluent: first, methylene chloride and then a 1 : 9 by volume mixture of methanol and methylene chloride), to afford 3.4 g of the title compound as a colourless amorphous substance.

9(b) Cyclostatin-(2-morpholinoethyl)amidedihydrochloride

3.4 g of N-t-butoxycarbonyl-cyclostatin-2-morpholinoethylamide were added to 30 ml of methanol and 30 ml of a IN solution of hydrogen chloride in dioxane. The mixture was stirred at room temperature for 1 hour, after which it was concentrated by evaporation under reduced pressure. The residue was washed with diethyl ether, to give 3.7 g of the title compound as colourless fine crystals melting at 70 - 80 °C.

PREPARATION 10

(2R)-3-(1-Naphthyl)-2-[(4-phenyl-1-piperazinyl)carbonylmethyl]propionic acid

10(a) (4S)-4-Benzyl-3-[(2R)-3-(1-naphthyl)-2-[(4-phenyl-1-piperazinyl)carbonylmethyl]propionyl]-2-oxazolidinone

Following a procedure similar to that described in Preparation 3, 230 mg of the title compound were prepared as a white powder from 340 mg (0.67 mmole) of N-[(2-benzyloxycarbonyl)methyl-3-(1-naphthyl)-propionyl]-(S)-(-)-4-benzyl-2-oxazolidinone (prepared as described in Preparation 2).

10(b) (2R)-3-(1-Naphthyl)-2-[(4-phenyl-1-piperazinyl)carbonylmethyl]propionic acid

Following a procedure similar to that described in Preparation 4, 103 mg of the hemihydrate of the title compound were prepared as a white powder from 0.21 g (0.37 mmole) of (4S)-4-benzyl-3-[(2R)-3-(1-naphthyl)-2-[(4-phenyl-1-piperazinyl)carbonylmethyl]propionyl]-2-oxazolidinone [prepared as described in Preparation 10(a)].
Mass Spectrum m/e: 402 (M^+).

Elemental analysis:

Calculated for $C_{25}H_{26}N_2O_3 \cdot {}^1/_2\ H_2O$:						
Found:	C,	72.97%;	H,	6.61%;	N,	6.81%.
	C,	72.68%;	H,	6.62%;	N,	6.67%.

PREPARATION 11

4-Morpholinocarbonyl-2-(1-naphthylmethyl)butyric acid

8.17 g (0.19 mole) of sodium hydride (as a 55% w/w dispersion in mineral oil) were added, whilst ice-cooling, to a solution of 25 g (0.16 mole) of dimethyl glutarate and 23.4 g (0.16 mole) of 1-naphthaldehyde dissolved in 200 ml of anhydrous methanol. The mixture was heated under reflux for 30 minutes, after which 190 ml (0.19 mol) of a IN aqueous solution of sodium hydr xide were added to it, and th mixture was again heated und r r flux for 1 hour. The solvent was removed by distillation under reduced pr ssure, and th r sulting residue was mixed with water and washed with diethyl eth r. The aqueous layer was acidified and then extracted with diethyl ther. The ethereal layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and then diisopropyl ether was added to the r sidu to precipitat crystals, which were collected by filtration to giv 18.5 g of 2-(1-naphthylmethylene)glutaric acid.

A mixture of 10 g (37 mmole) of the 2-(1-naphthylmethylene)glutaric acid prepared as described above and 100 ml of acetic anhydride was stirred at 60°C for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressur , and the resulting residue was triturated with a 1 : 1 by volume mixture of benzene and hexane to precipitate crystals, which were collected by filtration to give 8.1 g of 2-(1-naphthylmethylene)glutaric anhydride.

2.85 ml (33 mmole) of morpholine were added to a solution of 7.5 g (30 mmole) of the 2-(1-naphthylmethylene)glutaric anhydride prepared as described above dissolved in 70 ml of methylene chloride, and the mixture was stirred at room temperature for 4 hours. It was then washed with a 5% w/v aqueous solution of citric acid and with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, to give 10.0 g (30 mmole) of 4-morpholinocarbonyl-2-(1-naphthylmethylene)butyric acid.

5.0 g (14.8 mmole) of this 4-morpholinocarbonyl-2-(1-naphthylmethylene)butyric acid were dissolved in 50 ml of methanol and hydrogenated in hydrogen at atmospheric pressure in the presence of 1.0 g of a 10% w/w palladium-on-carbon catalyst. The catalyst was then removed by filtration, after which the solvent was removed by distillation under reduced pressure. The residue was triturated with diethyl ether to precipitate crystals, which were collected by filtration to give 4.5 g of 4-morpholinocarbonyl-2-(1-naphthylmethyl)butyric acid, melting at 130 - 135°C

Elemental analysis:

Calculated for $C_{20}H_{23}NO_4$:						
	C,	70.36%;	H,	6.79%;	N,	4.10%.
Found:	C,	70.06%;	H,	6.90%;	N,	3.98%.

PREPARATION 12

t-Butyl 5-(N-benzyl-N-methylamino)-4-hydroxy-2-(1-naphthylmethyl)pentanoate

2.39 g (7.65 mmole) of t-butyl 4,5-epoxy-2-(1-naphthylmethyl)pentanoate were reacted with 1.39 g (11.5 mmole) of N-methylbenzylamine in 20 ml of methanol for 2 days. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was purified by column chromatography through silica gel (eluent: a 5 : 95 by volume mixture of methanol and methylene chloride), to afford 3.13 g of the title compound as a pale brown oil.

PREPARATION 13

5-(N-Benzyl-N-methylamino)-2-(1-naphthylmethyl)-4-oxopentanoic acid

5.64 g of a sulphur trioxide/pyridine complex were added to a solution of 3.13 g (7.22 mmole) of t-butyl 5-(N-benzyl-N-methylamino)-4-hydroxy-2-(1-naphthylmethyl)pentanoate (prepared as described in Preparation 12) and 5 ml of triethylamine dissolved in 20 ml of dimethyl sulphoxide at room temperature, and the mixture was stirred for 2 hours. At the end of this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate, after which it was concentrated by evaporation under reduced pressure. 20 ml of a 4N solution of hydrogen chloride in dioxane were added to the residue, and the mixture was stirred for 2 hours; it was then concentrated by evaporation under reduced pressure. The residue was dissolved in water, and the resulting solution was neutralized by adding a 1N aqueous solution of sodium hydroxide. It was then concentrated by evaporation under reduced pressur . The r sidu was dissolved in methylen chlorid and th r sulting insolubl mat rials w r r moved by filtration. The filtrate was concentrated by evap ration under r duc d pressur to afford 1.94 g of the title compound as a colourl ss am rphous substanc .

Silica gel thin layer chromatography, Rf valu 0.55 (20% by volume methanol in methylene chloride).

PREPARATION 14

(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionic acid

14(a) (4S)-4-Isopropyl-3-[(3-(1-naphthyl)propionyl]-2-oxazolidinone

Following a procedure similar to that described in Preparation 1, 1.9 g (14.8 mmole) of (S)-(-)-4-isopropyl-2-oxazolidinone [instead of (S)-(-)-4-benzyl-2-oxazolidinone] were reacted with 2.95 g (13.5 mmole) of 1-naphthylpropionyl chloride to afford 3.2 g of the title compound as a white powder.

14(b) (4S)-4-Isopropyl-3-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-2-oxazolidinone

Following a procedure similar to that described in Preparation 2, 384 mg (1.3 mmole) of (4S)-3-[3-(1-naphthyl)propionyl]-4-isopropyl-2-oxazolidinone were reacted with 613 ml (3.87 mmole) of benzyl bromoacetate, and then the mixture was worked-up according to Preparation 3 to give 297 mg of the title compound as a white powder.

14(c) (2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionic acid

Following a procedure similar to that described in Preparation 4, 825 mg of the title compound were prepared as a white powder from 1.42 g (3.0 mmole) of (4S)-4-isopropyl-3-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-2-oxazolidinone [prepared as described in Preparation 14(b)].
Mass Spectrum m/e: 361 (M^+).

PREPARATION 15

Methyl N-(4-phenyl-1-piperazinylacetyl)-3-(1-naphthyl)-L-alanate hydrochloride

266 mg of methyl 3-(1-naphthyl)-L-alanate hydrochloride, 221 mg of (4-phenyl-1-piperazinyl)acetic acid and 0.35 ml of triethylamine were added to 5 ml of dimethylformamide , and then 200 mg of diethyl cyanophosphonate (90%) were added dropwise, whilst ice-cooling, to the mixture. The mixture was then stirred for 4 hours, after which it was allowed to stand overnight. The reaction mixture was then concentrated by evaporation under reduced pressure, and water was added to the residue, which was then extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 1 : 9 by volume mixture of methanol and methylene chloride), to afford 278 mg of the title compound as an oily substance.

PREPARATION 16

N-(4-Phenyl-1-piperazinylacetyl)-3-(1-naphthyl)-L-alanine

1.2 ml of a 1N aqueous solution of sodium hydroxide was added to a solution of 250 mg of methyl (4-phenyl-1-piperazinyl)acetyl-3-(1-naphthyl)-L-alanate hydrochloride (prepared as described in Preparation 15) in 8 ml of methanol, and the mixture was stirred at room temperature for 2 hours. At the end of this time, 1.2 ml of 1N aqueous hydrochloric acid was added to the reaction mixture, which was then concentrated by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 15 : 85 by volume mixture of methanol and methylene chloride), to afford 220 mg of the title compound as colourless powdery crystals, melting at 160 - 180 °C.

PREPARATION 17

N-Morpholinoac tyl-3-(1-naphthyl)-L-alanin

7.8 g (64.6 mmole) of diph nylphosphoryl azide and 17.9 ml (129.1 mmole) of triethylamin wer added, whilst ice-cooling, to a solution of 7.8 g (53.8 mmole) of 1-morpholinoacetic acid and 15.7 g (59.2

mmole) of methyl 3-(1-naphthyl)-L-alanat hydrochloride in 80 ml of dimethylformamide, and the mixture was stirred at room temperature overnight. At the end of this time, 300 ml of a saturated aqueous solution of sodium chloride were added to the reaction mixture, which was then extracted with ethyl acetate. The xtract was then washed with a 5% w/v aqueous solution of citric acid, with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: mixtures of methylene chloride and methanol in the propartions by volume 70 : 1 and 30 : 1), to afford 9.8 g of methyl N-morpholinoacetyl-3-(1-naphthyl)-L-alanate as an oily substance.

19.6 ml (19.6 mmole) of a 1N aqueous solution of sodium hydroxide were then added to a solution of 7.0 g (19.6 mmole) of this methyl N-morpholinoacetyl-3-(1-naphthyl)-L-alanate in 50 ml of methanol, and the mixture was stirred at room temperature for 1 hour. At the end of this time, 4.9 ml (19.6 mmole) of a 4N solution of hydrogen chloride in dioxane was added to the reaction mixture, and the mixture was extracted with methylene chloride. The organic extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The solvent was then removed by evaporation under reduced pressure, and the residue was crystallized by the addition of diethyl ether, to give 6.25 g of the title compound, melting at 100 - 103 °C.

PREPARATION 18

N-[N-(t-Butoxycarbonyl)-L-leucyl]-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide

1.37 g (5.5 mmole) of N-(t-butoxycarbonyl)-L-leucine hydrate was dehydrated by repeating 2 - 3 times the steps of dissolution in methanol followed by azeotropic distillation. Meanwhile, the t-butoxycarbonyl group was removed from 2.20 g (5 mmole) of N-(t-butoxycarbonyl)-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)-propyl]amide by treatment with a 4N solution of hydrogen chloride in dioxane. The two compounds thus obtained were dissolved together in 25 ml of methylene chloride, and then 1.03 g (6 mmole) of diethyl cyanophosphonate (95%) and 2.02 g (20 mmole) of triethylamine were added to the resulting solution, and the mixture was stirred, whilst ice-cooling for 1 hour; this stirring was continued at room temperature for 3 days. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a 10% w/v aqueous solution of citric acid, with water and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in methylene chloride, insoluble materials were removed by filtration, and the filtrate was concentrated by evaporation under reduced pressure. The residue was triturated with diethyl ether, to afford 12.25 g of the 0.25-hydrate of the title compound, melting at 170 - 173 °C.

Elemental analysis:

Calculated for $C_{29}H_{52}N_4O_6 \cdot {}^1/_4\ H_2O$:						
Found:	C,	62.50%;	H,	9.50%;	N,	10.06%.
	C,	62.40%;	H,	9.46%;	N,	10.04%.

PREPARATION 19

N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine

19(a) Methyl N-(N-benzyl-N-m thylaminoac tyl)-3-(1-naphthyl)-L-alanat

53 mg (0.5 mmol) of sodium carbonate were added to a solution of 350 mg (1.0 mmole) of m thyl N-bromoacetyl-3-(1-naphthyl)-L-alanate and 121 mg (1.0 mmole) of N-benzyl-N-methylamine in 15 ml of dimethylformamide, and the mixture was stirred at room temperature for 10 hours. At the nd of this time, th solvent was removed by distillation under r duced pressure, and th r sidue, after the addition of a small amount of wat r, was extracted with ethyl acetate. Th xtract was dried over anhydrous sodium

sulphate and concentrated by evaporation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: a 10 : 1 by volume mixture of chloroform and methanol), to afford 280 mg of the title compound as an oily substanc .

19(b) N-(Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine

1.92 ml (1.92 mmole) of a 1N aqueous solution of sodium hydroxide was added to a solution of 250 mg (0.64 mmole) of methyl N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanate [prepared as described in step (a) above] in 2 ml of methanol, and the mixture was stirred at room temperature for 4 hours. At the end of this time, the reaction mixture was neutralized by the addition of 1.92 mg (1.92 mmole) of 1N aqueous hydrochloric acid, and the methanol was removed by evaporation under reduced pressure. The residue was extracted with ethyl acetate, the extract was dried, and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: a 5 : 1 by volume mixture of chloroform and methanol), to afford 171 mg of the title compound as white crystals, melting at 104 - 107°C.

PREPARATION 20

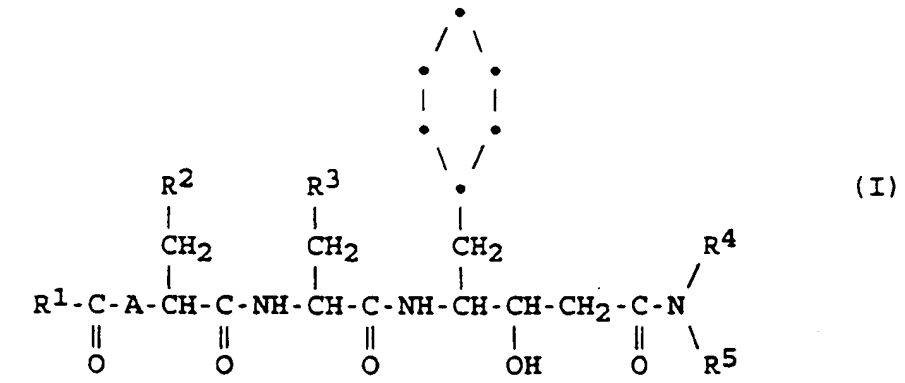
N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanine

A solution of 5 g (14.3 mmole) of methyl N-bromoacetyl-3-(1-naphthyl)-L-alanate [prepared as described in Example 21(a)] and 6.5 g (57.5 mmole) of N-cyclohexyl-N-methylamine in 50 ml of dimethylformamide was stirred at 50°C for 3 hours. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a 2% w/v aqueous solution of citric acid (3 times), with water, with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 30 ml of a 1N solution of sodium hydroxide in 90% v/v aqueous methanol, and the solution was stirred at room temperature for 3 hours. At the end of this time, the reaction mixture was neutralized by the addition of 30 ml of 1N aqueous hydrochloric acid and concentrated by evaporation under reduced pressure. The mixture was then diluted with methanol, the sodium chloride produced was removed by filtration, the filtrate was again concentrated by evaporation under reduced pressure, and the residue was triturated with hexane, to afford 5.5 g of the title compound as a white powder, melting at 72 - 77°C.

Claims

Claims for the following Contracting States : AT, GB, DE, FR, IT, CH, BE, NL, SE, LU, LI

1. Compounds of formula (I):



(I)

wh rein:

R^1 represents a 4-phenyl-1-piperazinyl, N-methyl-N-benzylamino, morpholino, N-methyl-N-cyclohexylaminomethyl N-methyl-N-benzylaminomethyl, N-isopropyl-N-benzylaminom thyl, benzylaminom thyl,

4-phenyl-1-piperazinylmethyl, diethylaminomethyl N-methyl-N-butylaminom thyl, N-methyl-N-phenylaminomethyl, morpholinomethyl, 3-morpholinopropyl, 4-(4-fluorophenyl)-1-piperazinylmethyl, 4-(4-chlorophenyl)-1-piperazinylmethyl, 4-(4-methoxyphenyl)-1-piperazinylmethyl, N-methyl-N-phenethylaminomethyl, diisobutylaminomethyl or 4-(4-chlorobenzhydryl)-1-piperazinylmethyl group;
R^2 represents a naphthyl group;
R^3 represents a thienyl, isoxazolyl, thiazolyl, imidazolyl or isopropyl group;
R^4 represents a 2-morpholinoethyl, propyl, butyl, isobutyl, pentyl, isopentyl, 2-methylbutyl, hexyl, 3-(2-oxo-1-pyrrolidinyl)propyl or 1-morpholinomethyl-2-methylbutyl group;
R^5 represents a hydrogen atom or a C_1 - C_8 alkyl group; and
A represents a group of formula -NH- or $(CH_2)_n$-, in which n represents 1 or 2,
WITH THE PROVISO THAT when R^1 represents a benzylaminomethyl group, R^3 represents a thienyl, isoxazolyl or thiazolyl group.

2. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

3. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

4. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

5. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

6. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

7. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

8. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

9. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide and pharmaceutically acceptable salts thereof.

10. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[-(S)-2-methylbutyl]amide and pharmaceutically acceptable salts thereof.

11. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

12. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

13. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

14. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

15. N-{N-[N-(N-Cyclohexyl-N-m thylaminoacetyl)-3-(1-naphthyl)-alanyl]-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts th reof.

16. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

17. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-imidazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

18. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

19. N-[N-{N-[4-(4-Chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-alanyl}-3-(4-thiazolyl)-alanyl]-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

20. N-[N-{N-[4-(4-Chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

21. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

22. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

23. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

24. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

25. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amide and pharmaceutically acceptable salts thereof.

26. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide and pharmaceutically acceptable salts thereof.

27. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]amide and pharmaceutically acceptable salts thereof.

28. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-isobutylamide and pharmaceutically acceptable salts thereof.

29. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-propylamide and pharmaceutically acceptable salts thereof.

30. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-butylamide and pharmaceutically acceptable salts thereof.

31. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-pentylamide and pharmaceutically acceptable salts thereof.

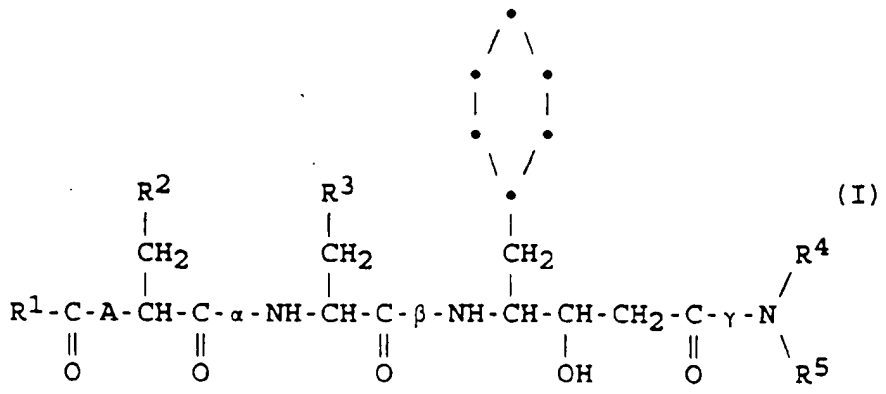
32. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-isopentylamide and pharmaceutically acceptable salts thereof.

33. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-hexylamide and pharmaceutically acceptable salts thereof.

34. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamid and pharmaceutically acceptable salts th reof.

35. A composition for the tr atment of angiotensin-induced hypertension in a mammal, which comprises an antihypertensiv ag nt in admixtur with a pharmaceutically acceptabl carrier or dilu nt, wherein said antihypert nsiv agent is at least one compound according to any on of the preceding Claims.

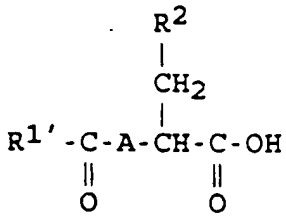
36. A process for preparing a compound according to any one of Claims 1 to 34, which process comprises reacting together two compounds, one having a terminal carboxy group or reactive derivative thereof and the other having a terminal amino group or reactive derivative thereof, under peptide synthesis conditions, said two compounds corresponding to the fragments derivable by cleavag of any one of the peptide bonds marked α, βand γ in the following formula (I) and, where A is a group -NH-, between that group and the adjacent carboxy group:



(I)

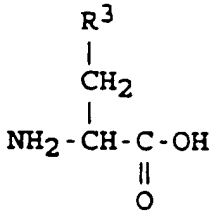
(in which R^1 - R^5 and A are as defined in Claim 1) or a compound of formula (I) in which a reactive group or groups has or have been protected, and, if necessary, deprotecting and/or salifying the resulting compound.

37. A process according to Claim 36, which comprises:
reacting together compounds of formulae:



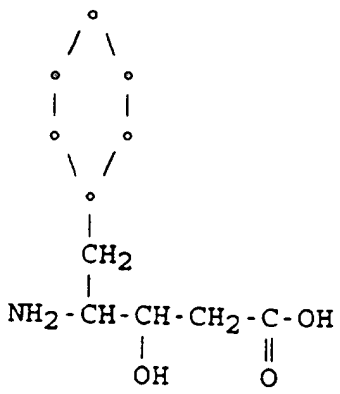
(IV)

or a reactive derivative thereof,



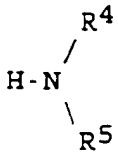
(V)

or a reactive derivative thereof,



(VI)

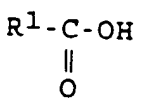
or a reactive derivative thereof, and



(VII)

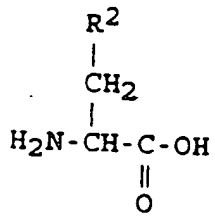
or a reactive derivative thereof (in the above formulae R^2 - R^5 and A are as defined in Claim 1 and $R^{1'}$ represents any of the groups represented by R^1, as defined in Claim 1, or an active group), and, where $R^{1'}$ represents said active group, converting it to any one of the groups represented by R^1;
or reacting a peptide compound derivable by reaction of some of said compounds of formulae (IV), (V), (VI) or (VII) or said reactive derivatives with the remainder of said compounds or said reactive derivative(s) or with a peptide compound or compounds derivable by reaction of said remainder or reactive derivative(s) thereof, the reaction(s) being in an order corresponding to the order of the residues derived from said compounds of formulae (IV), (V), (VI) and (VII) in said compound of formula (I).

38. A process according to Claim 37, in which A represents a group of formula -NH- and the compound of formula (IV) is replaced by the two compounds of formulae (IVa) and (IVb):



(IVa)

and

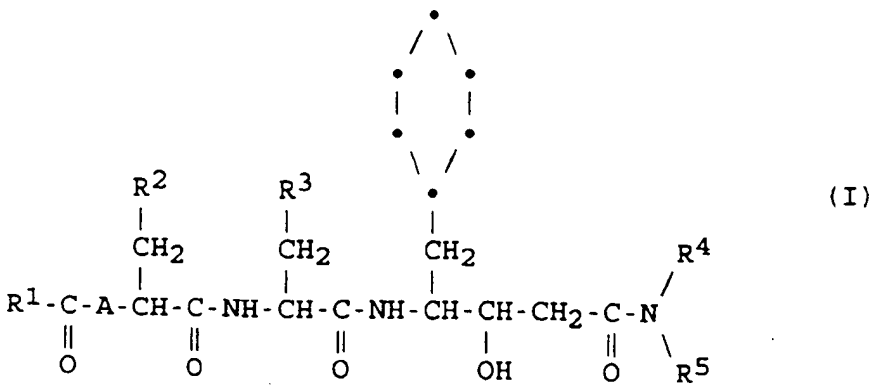


(IVb)

(in which R^1 and R^2 are as defined in Claim 1).

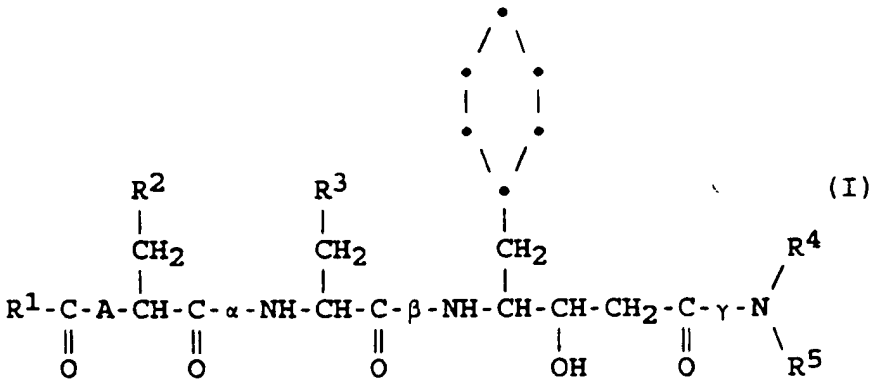
Claims for the following Contracting States : ES, GR

1. A process for preparing compounds of formula (I):



(I)

[wherein:
R^1 represents a 4-phenyl-1-piperazinyl, N-methyl-N-benzylamino, morpholino, N-methyl-N-cyclohexylaminomethyl, N-methyl-N-benzylaminomethyl, N-isopropyl-N-benzylaminomethyl, benzylaminomethyl, 4-phenyl-1-piperazinylmethyl, diethylaminomethyl, N-methyl-N-butylaminomethyl, N-methyl-N-phenylaminomethyl, morpholinomethyl, 3-morpholinopropyl, 4-(4-fluorophenyl)-1-piperazinylmethyl, 4-(4-chlorophenyl)-1-piperazinylmethyl, 4-(4-methoxyphenyl)-1-piperazinylmethyl, N-methyl-N-phenethylaminomethyl, diisobutylaminomethyl or 4-(4-chlorobenzhydryl)-1-piperazinylmethyl group;
R^2 represents a naphthyl group;
R^3 represents a thienyl, isoxazolyl, thiazolyl, imidazolyl or isopropyl group;
R^4 represents a 2-morpholinoethyl, propyl, butyl, isobutyl, pentyl, isopentyl, 2-methylbutyl, hexyl, 3-(2-oxo-1-pyrrolidinyl)propyl or 1-morpholinomethyl-2-methylbutyl group;
R^5 represents a hydrogen atom or a C_1 - C_8 alkyl group; and
A represents a group of formula -NH- or $-(CH_2)_n-$, in which n represents 1 or 2,
WITH THE PROVISO THAT when R^1 represents a benzylaminomethyl group, R^3 represents a thienyl, isoxazolyl or thiazolyl group];
and pharmaceutically acceptable salts thereof, which process comprises:
reacting together two compounds, one having a terminal carboxy group or reactive derivative thereof and the other having a terminal amino group or reactive derivative thereof, under peptide synthesis conditions, said two compounds corresponding to the fragments derivable by cleavage of any one of the peptide bonds marked α, β and γ in the following formula (I) and, where A is a group -NH-, between that group and the adjacent carboxy group:

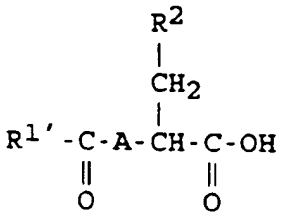


(I)

(in which R^1 - R^5 and A are as defined above) or a compound of formula (I) in which a reactive group or groups has or have been protected; and

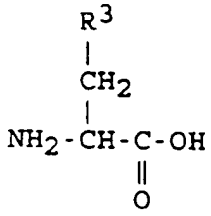
if necessary, deprotecting and/or salifying the resulting compound.

2. A process according to Claim 1, in which:
there are reacted together compounds of formulae:



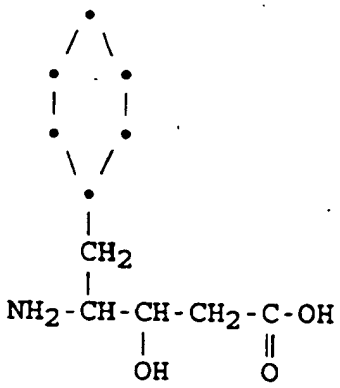
(IV)

or a reactive derivative thereof,



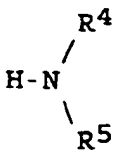
(V)

or a reactive derivative thereof,



(VI)

or a reactive derivative thereof, and

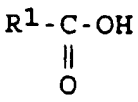


(VII)

or a reactive derivative thereof (in the above formulae R^2 - R^5 and A are as defined in Claim 1 and $R^{1'}$ represents any of the groups represented by R^1, as defined in Claim 1, or an active group), and where $R^{1'}$ represents said active group, it is converted to any one of the groups represented by R^1;

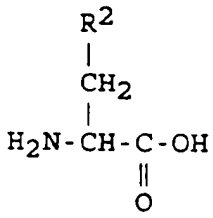
3. A process according to Claim 2, in which th re are reacted a peptide compound derivable by reaction of some of said compounds of formulae (IV), (V), (VI) or (VII), as defined in Claim 2, or said reactive derivatives with the r mainder of said compounds or said reactiv derivative(s) or with a peptide compound or compounds derivable by reaction of said remainder or reactive derivative(s) thereof, the reaction(s) being in an order corresponding to the order of the residues derived from said compounds of formulae (IV), (V), (VI) and (VII) in said compound of formula (I).

4. A process according to Claim 2 or Claim 3, in which A represents a group of formula -NH- and the compound of formula (IV) is replaced by the two compounds of formulae (IVa) and (IVb):



(IVa)

and



(IVb)

(in which R^1 and R^2 are as defined in Claim 1).

5. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

6. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

7. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

8. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

9. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

10. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-alanyl}cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

11. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[(2R)-3-(N-benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

12. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide and pharmaceutically acceptable salts thereof.

13. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatin-[(S)-2-methylbutyl]amide and pharmaceutically acceptable salts thereof.

14. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

15. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

16. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-methylanilinoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

17. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-methylanilinoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

18. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

19. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

20. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-imidazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

21. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

22. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-[N-{N-[4-(4-chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-alanyl}-3-(4-thiazolyl)-alanyl]-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

23. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-[N-{N-[4-(4-chlorobenzhydryl)-1-piperazinylacetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

24. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts thereof.

25. A process according to Claim 1, wh rein the reagents and conditions are so chos n as to pr pare N-{N-[N-(N-benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)amide and pharmaceutically acceptable salts th reof.

26. A process according to Claim 1, wherein the reag nts and conditions are so chosen as to prepar N-{N-[N-(N-cycloh xyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-

(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

27. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-(N-benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]amide and pharmaceutically acceptable salts thereof.

28. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide and pharmaceutically acceptable salts thereof.

29. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)amide and pharmaceutically acceptable salts thereof.

30. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]-amide and pharmaceutically acceptable salts thereof.

31. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl]-cyclostatin-isobutylamide and pharmaceutically acceptable salts thereof.

32. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-propylamide and pharmaceutically acceptable salts thereof.

33. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-butylamide and pharmaceutically acceptable salts thereof.

34. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-pentylamide and pharmaceutically acceptable salts thereof.

35. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-isopentylamide and pharmaceutically acceptable salts thereof.

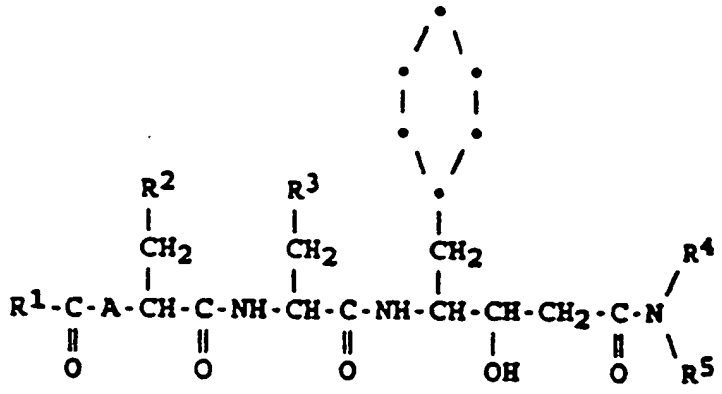
36. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-hexylamide and pharmaceutically acceptable salts thereof.

37. A process according to Claim 1, wherein the reagents and conditions are so chosen as to prepare N-{N-[N-morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamide and pharmaceutically acceptable salts thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : GB, DE, FR, IT, CH, BE, NL, SE, LU, AT, LI

1. Verbindungen der Formel (I):



(I)

worin
R^1 eine 4-Phenyl-1-piperazinyl-, N-Methyl-N-benzylamino-, Morpholino-, N-Methyl-N-cyclohexylaminomethyl-, N-Methyl-N-benzylaminomethyl-, N-Isopropyl-N-benzylaminomethyl-, Benzylaminomethyl-, 4-Phenyl-1-piperazinylmethyl-, Diethylaminomethyl-, N-Methyl-N-butylaminomethyl, N-Methyl-N-phenylaminomethyl-, Morpholinomethyl-, 3-Morpholinopropyl-, 4-(4-Fluorphenyl)-1-piperazinylmethyl-, 4-(4-Chlorphenyl)-1-piperazinylmethyl-, 4-(4-Methoxyphenyl)-1-piperazinylmethyl-, N-Methyl-N-phenethylaminomethyl-, Diisobutylaminomethyl- oder 4-(4-Chlorbenzhydryl)-1-piperazinylmethylgruppe bedeuten,
R^2 eine Naphthylgruppe darstellt;
R^3 eine Thienyl- Isoxazolyl-, Thiazolyl-, Imidazolyl- oder Isopropylgruppe bedeutet;
R^4 eine 2-Morpholinoethyl-, Propyl-, Butyl-, Isobutyl-, Pentyl-, Isopentyl-, 2-Methylbutyl-, Hexyl-, 3-(2-Oxo-1-pyrrolidinyl)-propyl- oder 1-Morpholinomethyl-2-methylbutylgruppe bedeutet,
R^5 ein Wasserstoffatom oder eine C_1-C_8-Alkylgruppe bedeutet, und
A eine Gruppe der Formel -NH- oder $-(CH_2)_n-$ darstellt, worin n 1 oder 2 bedeutet,
mit der Maßgabe, daß dann, wenn R^1 eine Benzylaminomethylgruppe darstellt, R^3 eine Thienyl-, Isoxazolyl- oder Thiazolylgruppe bedeutet.

2. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

3. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

4. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

5. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

6. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

7. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dess n pharmazeutisch g eign te Salze.

8. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholino thyl)-amid und dess n pharmazeutisch geeignete Salze.

9. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amid und dessen pharmazeutisch geeignete Salze.

10. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[-(S)-2-methylbutyl]-amid und dessen pharmazeutisch geeignete Salze.

11. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

12. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

13. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)alanyl]-3-(4-thiazolyl)-alanyl-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

14. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl)-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

15. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

16. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

17. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-imidazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

18. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

19. N-[N-{N-[4-(4-Chlorbenzhydryl)-1-piperazinyl-acetyl]-3-(1-naphthyl)-alanyl}-3-(4-thiazolyl)-alanyl]-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

20. N-[N-{N-[4-(4-Chlorbenzhydryl)-1-piperazinyl-acetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

21. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

22. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

23. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

24. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

25. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(5-isoxazolyl)-alanyl]-cyclostatin-(2-methylbutyl)-amid und dessen pharmazeutisch geeignete Salze.

26. N-{N-[N-Morpholinoac tyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-(2-m thylbutyl)-amid und dess n pharmazeutisch geeignete Salz .

27. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]-amid und dess n pharmaz utisch g ignete Salze.

28. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-isobutylamid und dessen pharmazeutisch geeignete Salze.

29. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-propylamid und dessen pharmazeutisch geeignete Salze.

30. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-butylamid und dessen pharmazeutisch geeignete Salze.

31. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl]-cyclostatin-pentylamid und dessen pharmazeutisch geeignete Salze.

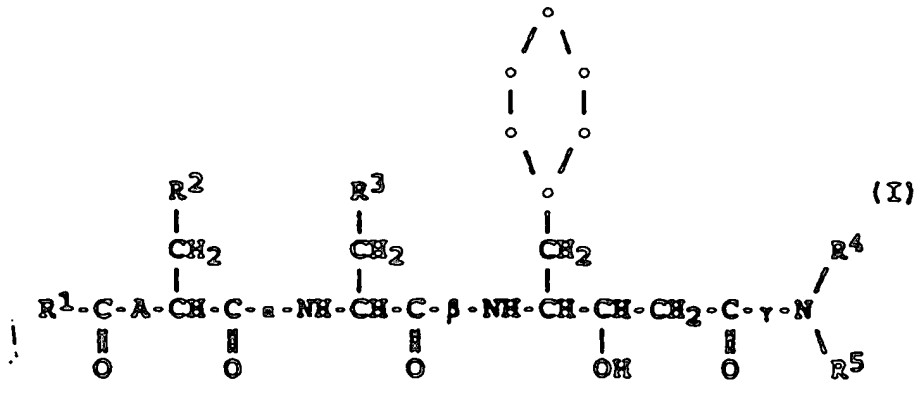
32. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-isopentylamid und dessen pharmazeutisch geeignete Salze.

33. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-hexylamid und dessen pharmazeutisch geeignete Salze.

34. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl] -3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamid und dessen pharmazeutisch geeignete Salze.

35. Zusammensetzung zur Behandlung von Angiotensininduzierter Hypertension in einem Säuger, die ein antihypertensives Mittel im Gemisch mit einem pharmazeutisch geeigneten Trägermaterial oder Verdünnungsmittel enthält, worin das antihypertensive Mittel mindestens eine Verbindung gemäß einem der vorhergehenden Patentansprüche ist.

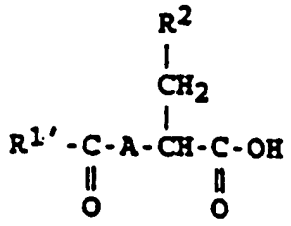
36. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 34, das darin besteht, daß zwei Verbindungen, deren eine eine endständige Carboxylgruppe oder ein reaktives Derivat davon, und deren andere eine endständige Aminogruppe oder ein reaktives Derivat davon enthält, unter Bedingungen der Peptidsynthese miteinander umgesetzt werden, wobei die beiden Verbindungen den Fragmenten entsprechen, die durch Spaltung einer der mit α, β und γ in der folgenden Formel (I) bezeichneten Peptidbindungen und, falls A eine Gruppe -NH- ist, zwischen dieser Gruppe und der benachbarten Carboxylgruppe



(I)

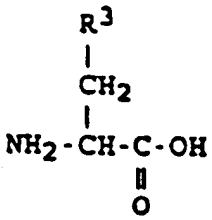
(n der R^1-R^5 und A wie in Anspruch 1 definiert sind) oder einer Verbindung der Formel (I), in der reaktive Gruppe oder reaktive Gruppen geschützt ist bezi hungsweise sind, erhältlich sind und, erforderlichenfalls di resultier nde Verbindung ein r Schutzgruppenabspaltung und/oder Salzbildung unterworfen wird.

37. Verfahren gemäß Anspruch 36, das darin besteht, daß Verbindungen der Formeln



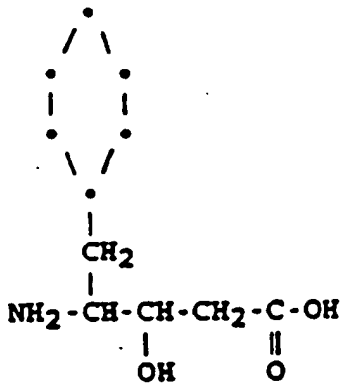
(IV)

oder ein reaktives Derivat davon,



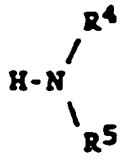
(V)

oder ein reaktives Derivat davon,



(VI)

oder ein reaktives Derivat davon, und

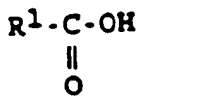


(VII)

oder in reaktives Derivat davon
miteinander umgesetzt werden (wobei in den vorstehenden Form In R^2 bis R^5 und A wie in Anspruch 1 definiert sind und $R^{1'}$ irgendeine der für R^1 in Anspruch 1 definierten Gruppen oder in aktiv Gruppe bedeutet) und, wenn $R^{1'}$ di se aktive Gruppe darstellt, di s in irgendeine der durch R^1 darg stellten Gruppen umgewandelt wird,
oder daß eine Peptidverbindung, die rhältlich ist durch Reaktion inig r der Verbindungen der Formeln (IV), (V), (VI) reaktiver Derivate mit dem verbl ibenden Anteil di ser V rbindungen od r dem reaktiven

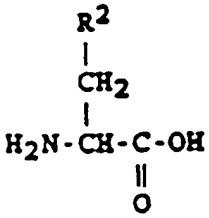
Derivat beziehungsweise den reaktiven Derivaten oder mit einer Peptidverbindung oder Peptidverbindungen umgesetzt wird, die durch Umsetzung des restlichen Anteils dieser Verbindungen oder deren reaktiven Derivat(en) herleitbar sind, wobei die Reaktion(en) in der Reihenfolge stattfindet beziehungsweise stattfinden, die der Anordnung der von den Verbindungen der Formeln (IV), (V), (VI) und (VII) abgeleiteten Reste in der Verbindung der Formel (I) entspricht.

38. Verfahren gemäß Anspruch 37, wobei A eine Gruppe der Formel -NH- darstellt und die Verbindung der Formel (IV) durch die beiden Verbindungen der Formeln (IVa) und (IVb) ersetzt ist:



(IVa)

und

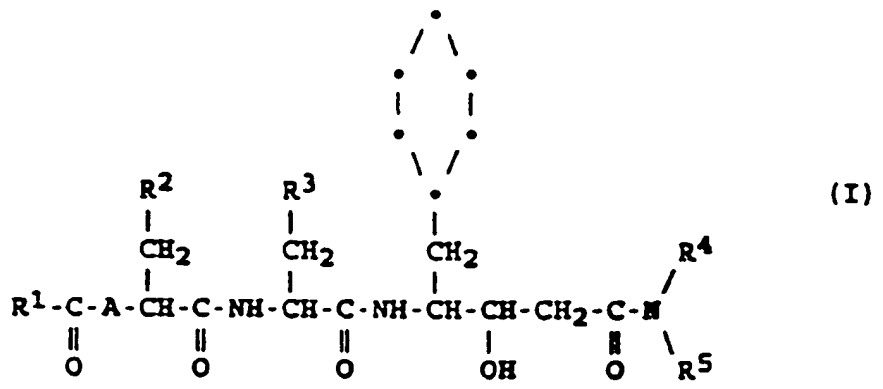


(IVb)

(worin R^1 und R^2 wie in Anspruch 1 definiert sind).

Patentansprüche für folgende Vertragsstaaten : ES, GR

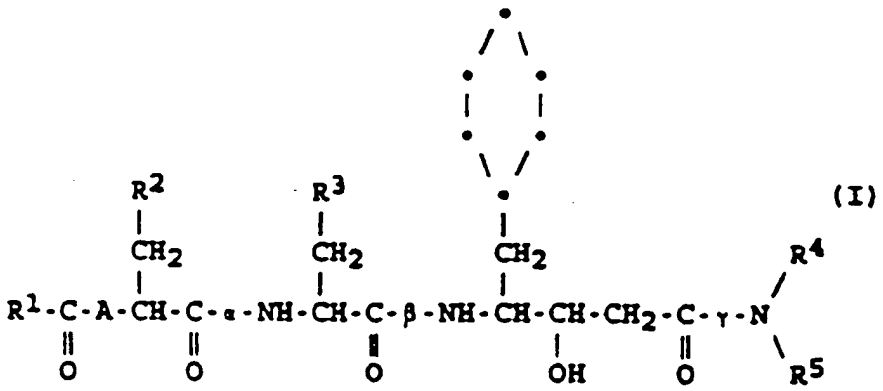
1. Verfahren zur Herstellung von Verbindungen der Formel (I):



(I)

[worin
R^1 eine 4-Phenyl-1-piperazinyl-, N-Methyl-N-benzylamino-, Morpholino-, N-Methyl-N-cyclohexylaminomethyl-, N-Methyl-N-b nzylaminomethyl-, N-Isopropyl-N-benzylaminomethyl-, Benzylaminom thyl-, 4-Phenyl-1-piperazinylm thyl-, Diethylaminomethyl-, N-Methyl-N-butylaminomethyl, N-Methyl-N-phenylaminom thyl-, Morpholinom thyl-, 3-Morpholinopr pyl-, 4-(4-Fluorph nyl)-1-piperazinylmethyl-, 4-(4-Chlorphenyl)-1-piperazinylmethyl-, 4-(4-Meth xyphenyl)-1-piperazinylmethyl-, N-Methyl-N-phenethylaminomethyl-, Diisobutylaminomethyl- od r 4-(4-Chlorbenzhydryl)-1-piperazinylmethylgruppe bedeuten,
R^2 in Naphthylgruppe darstellt;
R^3 ine Thienyl- Isoxazolyl-, Thiazolyl-, Imidazolyl- oder Isopropylgruppe bedeut t;

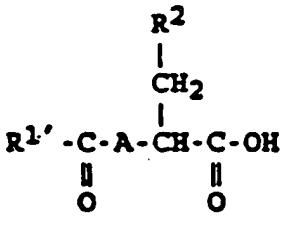
R^4 eine 2-Morpholinoethyl-, Propyl-, Butyl-, Isobutyl-, Pentyl-, Isopentyl-, 2-Methylbutyl-, Hexyl-, 3-(2-Oxo-1-pyrrolidinyl)-propyl-oder 1-Morpholinomethyl-2-methylbutylgruppe bedeutet,
R^5 ein Wasserstoffatom oder eine C_1-C_8-Alkylgruppe bedeutet, und
A eine Gruppe der Formel -NH- oder $-(CH_2)_n-$ darstellt, worin n 1 oder 2 bedeutet,
mit der Maßgabe, daß dann, wenn R^1 eine Benzylaminomethylgruppe darstellt, R^3 eine Thienyl-, Isoxazolyl- oder Thiazolylgruppe bedeutet],
und deren pharmazeutisch geeigneter Salze,
das darin besteht, daß zwei Verbindungen, deren eine eine endständige Carboxylgruppe oder ein reaktives Derivat davon, und deren andere eine endständige Aminogruppe oder ein reaktives Derivat davon enthält, unter Bedingungen der Peptidsynthese miteinander umgesetzt werden, wobei die beiden Verbindungen den Fragmenten entsprechen, die durch Spaltung einer der mit α, β und γ in der folgenden Formel (I) bezeichneten Peptidbindungen und, falls A eine Gruppe -NH- ist, zwischen dieser Gruppe und der benachbarten Carboxylgruppe



(I)

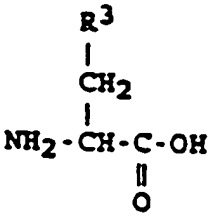
(n der R^1-R^5 und A wie oben definiert sind) oder einer Verbindung der Formel (I), in der eine reaktive Gruppe oder reaktive Gruppen geschützt ist beziehungsweise sind, erhältlich sind und, erforderlichenfalls die resultierende Verbindung einer Schutzgruppenabspaltung und/oder Salzbildung unterworfen wird.

2. Verfahren gemäß Anspruch 1, bei dem Verbindungen der Formeln



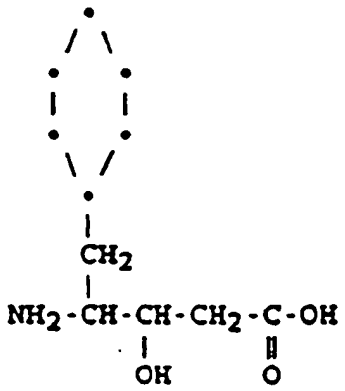
(IV)

oder ein reaktives Derivat davon,



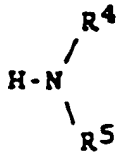
(V)

oder ein reaktives Derivat davon,



(VI)

oder ein reaktives Derivat davon, und

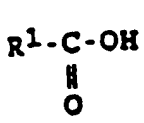


(VII)

oder ein reaktives Derivat davon
miteinander umgesetzt werden (wobei in den vorstehenden Formeln R^2 bis R^5 und A wie in Anspruch 1 definiert sind und $R^{1'}$ irgendeine der für R^1 in Anspruch 1 definierten Gruppen oder eine aktive Gruppe bedeutet) und, wenn $R^{1'}$ diese aktive Gruppe darstellt, diese in irgendeine der durch R^1 dargestellten Gruppen umgewandelt wird.

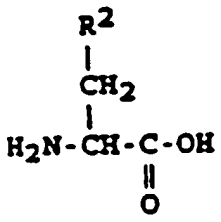
3. Verfahren gemäß Anspruch 2, bei dem eine Peptidverbindung, die durch Reaktion einiger der Verbindungen der Formeln (IV), (V), (VI) oder (VII) oder deren reaktiver Derivate mit dem verbleibenden Anteil dieser Verbindungen oder dem reaktiven Derivat beziehungsweise den reaktiven Derivaten oder mit einer Peptidverbindung oder Peptidverbindungen umgesetzt wird, die durch Umsetzung des restlichen Anteils dieser Verbindungen oder deren reaktiven Derivat(en) herleitbar sind, wobei die Reaktion(en) in der Reihenfolge stattfindet beziehungsweise stattfinden, die der Anordnung der von den Verbindungen der Formeln (IV), (V), (VI) und (VII) abgeleiteten Reste in der Verbindung der Formel (I) entspricht.

4. Verfahren gemäß Anspruch 2 oder Anspruch 3, wobei A eine Gruppe der Formel -NH- darstellt und die Verbindung der Formel (IV) durch die beiden Verbindungen der Formeln (IVa) und (IVb) ersetzt ist:



(IVa)

und



(IVb)

(worin R^1 und R^2 wie in Anspruch 1 definiert sind).

5. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

6. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-DL-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

7. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl)cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

8. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

9. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

10. N-{N-[3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

11. N-{N-[(2R)-3-(N-Benzyl-N-methylcarbamoyl)-2-(1-naphthylmethyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

12. N-{N-[3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amid und dessen pharmazeutisch geeignete Salze.

13. N-{N-[(2R)-3-Morpholinocarbonyl-2-(1-naphthylmethyl)propionyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[-(S)-2-methylbutyl]-amid und dessen pharmazeutisch geeignete Salze.

14. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

15. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

16. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)alanyl]-3-(4-thiazolyl)-alanyl-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

17. N-{N-[N-(N-Methylanilinoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl)-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

18. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

19. N-{N-[N-(N-Cyclohexyl-N-m thylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-L-leucyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

20. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-imidazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

21. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

22. N-[N-{N-[4-(4-Chlorbenzhydryl)-1-piperazinyl-acetyl]-3-(1-naphthyl)-alanyl}-3-(4-thiazolyl)-alanyl]-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

23. N-[N-{N-[4-(4-Chlorbenzhydryl)-1-piperazinyl-acetyl]-3-(1-naphthyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

24. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(4-thiazolyl)-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

25. N-{N-[N-(N-Benzyl-N-isopropylaminoacetyl)-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-(2-morpholinoethyl)-amid und dessen pharmazeutisch geeignete Salze.

26. N-{N-[N-(N-Cyclohexyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

27. N-{N-[N-(N-Benzyl-N-methylaminoacetyl)-3-(1-naphthyl)-alanyl]-3-(5-isoxazolyl)-alanyl}-cyclostatin-[3-(2-oxo-1-pyrrolidinyl)propyl]-amid und dessen pharmazeutisch geeignete Salze.

28. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(5-isoxazolyl)-alanyl]-cyclostatin-(2-methylbutyl)-amid und dessen pharmazeutisch geeignete Salze.

29. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-(2-methylbutyl)-amid und dessen pharmazeutisch geeignete Salze.

30. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}-cyclostatin-[(S)-2-methylbutyl]-amid und dessen pharmazeutisch geeignete Salze.

31. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-isobutylamid und dessen pharmazeutisch geeignete Salze.

32. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-propylamid und dessen pharmazeutisch geeignete Salze.

33. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-butylamid und dessen pharmazeutisch geeignete Salze.

34. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl]-cyclostatin-pentylamid und dessen pharmazeutisch geeignete Salze.

35. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-isopentylamid und dessen pharmazeutisch geeignete Salze.

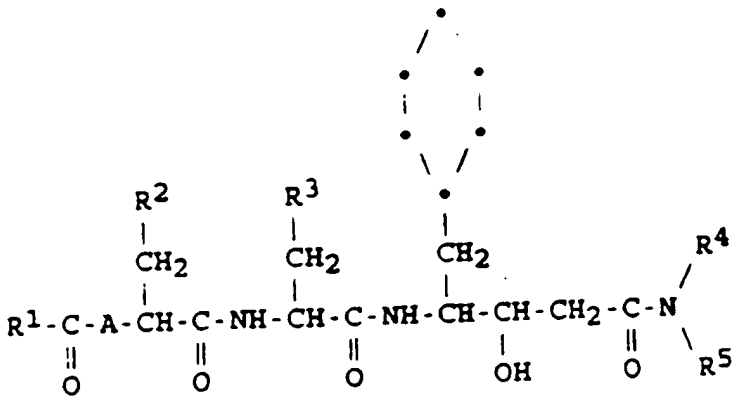
36. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-alanyl] -3-(4-thiazolyl)-alanyl}-cyclostatin-hexylamid und d ssen pharmazeutisch geeignete Salz .

37. N-{N-[N-Morpholinoacetyl-3-(1-naphthyl)-L-alanyl] -3-(4-thiazolyl)-L-alanyl}-cyclostatin-hexylamid und dessen pharmazeutisch g eignete Salze.

Revendications

Revendications pour les Etats contractants suivants : GB, DE, FR, IT, CH, BE, NL, SE, LU, AT, LI

1. Composés de formule (I) :



(I)

dans laquelle :
R^1 représente un groupe 4-phényl-1-pipérazinyle, N-méthyl-N-benzylamino, morpholino, N-méthyl-N-cyclohexylaminométhyle, N-méthyl-N-benzylaminométhyle, N-isopropyl-N-benzylaminométhyle, benzylaminométhyle, 4-phényl-1-pipérazinylméthyle, diéthylaminométhyle, N-méthyl-N-butylaminométhyle, N-méthyl-N-phénylaminométhyle, morpholinométhyle, 3-morpholinopropyle, 4-(4-fluorophényl)-1-pipérazinylméthyle, 4-(4-chlorophényl)-1-pipérazinylméthyle, 4-(4-méthoxyphényl)-1-pipérazinylméthyle, N-méthyl-N-phénéthylaminométhyle, diisobutylaminométhyle ou 4-(4-chlorobenzhydryl)-1-pipérazinylméthyle ;
R^2 représente un groupe naphtyle ;
R^3 représente un groupe thiényle, isoxazolyle, thiazolyle, imidazolyle ou isopropyle ;
R^4 représente un groupe 2-morpholinoéthyle, propyle, butyle, isobutyle, pentyle, isopentyle, 2-méthylbutyle, hexyle, 3-(2-oxo-1-pyrrolidinyl)propyle ou 1-morpholinométhyl-2-méthylbutyle ;
R^5 représente un atome d hydrogène ou un groupe alkyle en C_1-C_8 ; et
A représente un groupe de formule -NH- ou $-(CH_2)_n-$, dans laquelle n représente 1 ou 2,
sous réserve que lorsque R^1 représente un groupe benzylaminométhyle, R^3 représente un groupe thiényle, isoxazolyle ou thiazolyle.

2. N-{N-[3-morpholinocarbonyl-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

3. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-DL-alanyl)cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiqement acceptables.

4. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

5. N-{N-[3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

6. N-{N-[(2R)-3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amid et ses s ls pharmaceutiquement acceptables.

7. N-{N-[3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl) propionyl]-3-(5-isoxazolyl)-alanyl}cyclostatine-(2-morpholinoéthyl) amide et s s sels pharmac utiqu m nt acceptabl s.

8. N-{N-[(2R)-3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

9. N-{N-[3-morpholinocarbonyl-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-méthylbutyl)amide et ses sels pharmaceutiquement acceptables.

10. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-[-(S)-2-méthylbutyl] amide et ses sels pharmaceutiquement acceptables.

11. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(4-thiazolyl)alanyl)cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

12. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

13. N-{N-[N-(N-méthylanilinoacétyl)-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

14. N-{N-[N-(N-méthylanilinoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

15. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]leucyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl)propyl]amide et ses sels pharmaceutiquement acceptables.

16. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-L-leucyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl)propyl]amideet ses sels pharmaceutiquement acceptables.

17. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-imidazolyl)alanyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

18. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

19. N-[N-{N-[4-(4-chlorobenzhydryl)-1-pipérazinylacétyl]-3-(1-naphtyl)alanyl}-3-(4-thiazolyl)alanyl]-cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

20. N-[N-{N-[4-(4-chlorobenzhydryl)-1-pipérazinylacétyl]-3-(1-naphtyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

21. N-{N-[N-(N-benzyl-N-isopropylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(4-thiazolyl)alanyl)cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

22. N-{N-[N-(N-benzyl-N-isopropylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

23. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

24. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-(3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

25. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-(2-méthylbutyl)amide et ses sels pharmaceutiquement acceptables.

26. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatin -(2-méthylbutyl)amide et ses sels pharmaceutiqu ment acceptables.

27. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-[(S)-2-méthylbutyl]amide et ses sels pharmaceutiquement acceptables.

28. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-isobutylamide et ses sels pharmaceutiquement acceptables.

29. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-propylamide et ses sels pharmaceutiquement acceptables.

30. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-butylamide et ses sels pharmaceutiquement acceptables.

31. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-pentylamide et ses sels pharmaceutiquement acceptables.

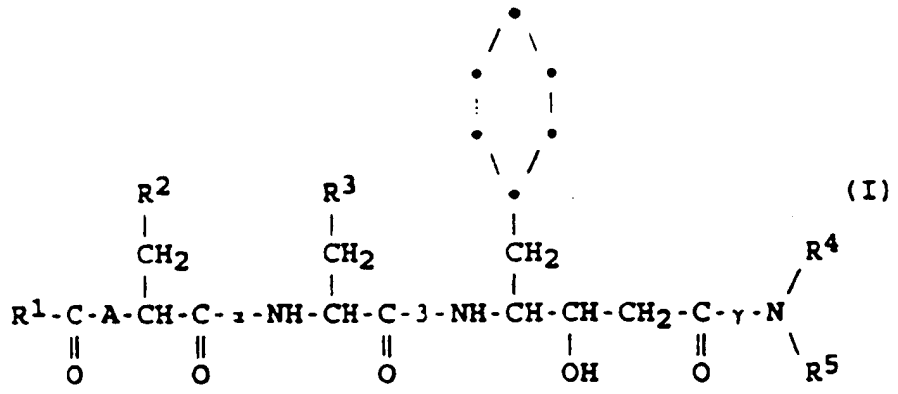
32. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-isopentylamide et ses sels pharmaceutiquement acceptables.

33. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-hexylamide et ses sels pharmaceutiquement acceptables.

34. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-hexylamide et ses sels pharmaceutiquement acceptables.

35. Composition pour le traitement de l'hypertension provoquée par l'angiotensine chez un mammifère, qui comprend un agent antihypertensif en mélange avec un véhicule ou diluant pharmaceutiquement acceptables, dans laquelle ledit agent antihypertensif est au moins un composé selon l'une une quelconque des revendications précédentes.

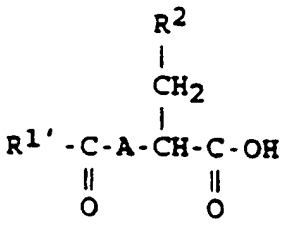
36. Procédé pour préparer un composé selon l'une quelconque des revendications 1 à 34, qui comprend la réaction mutuelle de deux composés, l'un ayant un groupe terminal carboxy ou un dérivé réactif de celui-ci et l'autre ayant un groupe terminal amino ou un dérivé réactif de celui-ci, dans des conditions de synthèse peptidique, lesdits deux composés correspondant aux fragments pouvant être obtenus par clivage de l'une quelconque des liaisons peptidiques marquées α, β et γ dans la formule (I) suivante dans laquelle A est un groupe -NH-, entre ce groupe et le groupe carboxy adjacent :



(I)

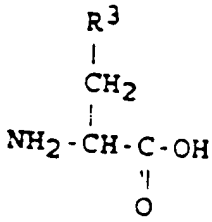
(dans laquelle R^1 à R^5 et A sont définis comme dans la r vendication 1) ou d'un composé d formule (I) dans laquelle un u plusieurs groupes réactifs ont été protégés, t, le cas échéant, la déprotection et/ou la salification du composé obtenu.

37. Procédé selon la revendication 36 qui comprend la réaction mutuelle des composés de formules :



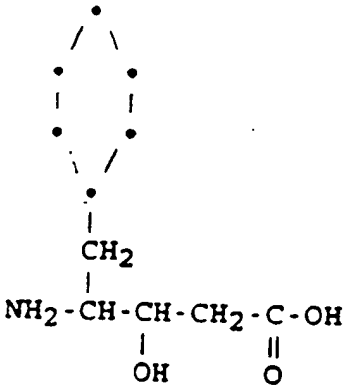
(IV)

ou d'un dérivé réactif de celui-ci,



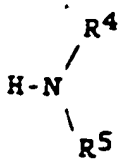
(V)

ou d'un dérivé réactif de celui-ci,



(VI)

ou d'un dérivé réactif de celui-ci, et

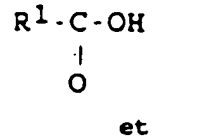


(VII)

ou d'un dérivé réactif de celui-ci (dans les formules ci-dessus, R^2 à R^5 et A sont définis comme dans la revendication 1 t $R^{1'}$ représ nte l'un quelconque des groupes représentés par R^1, définis comme dans la revendication 1, ou un groupe actif) et lorsque $R^{1'}$ représ nte ledit groupe actif, sa conversion en l'un quelconqu des groupes représentés par R^1 ;
ou la réaction d'un composé peptidique pouvant ˆtre obt nu par réaction de certains desdits composés de formules (IV), (V), (VI) ou (VII) ou desdits dérivés réactifs avec le r ste d sdits composés ou du ou desdits dérivé(s) réactif(s) ou avec un u plusieurs composés peptidiques pouvant êtr obtenus par réaction du rest desdits composés ou du ou d sdits dérivé(s) réactif(s) de ceux-ci, la ou les réaction(s)

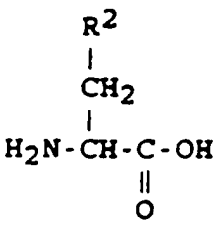
étant effectuée(s) dans un ordre correspondant à l'ordre des restes dérivés desdits composés de formules (IV), (V), (VI) et (VII) dans ledit composé de formul (I).

38. Procédé selon la revendication 37, dans lequel A représente un groupe de formule -NH- et le composé de formule (IV) est remplacé par deux composés de formules (IVa) et (IVb) :



(IVa)

et

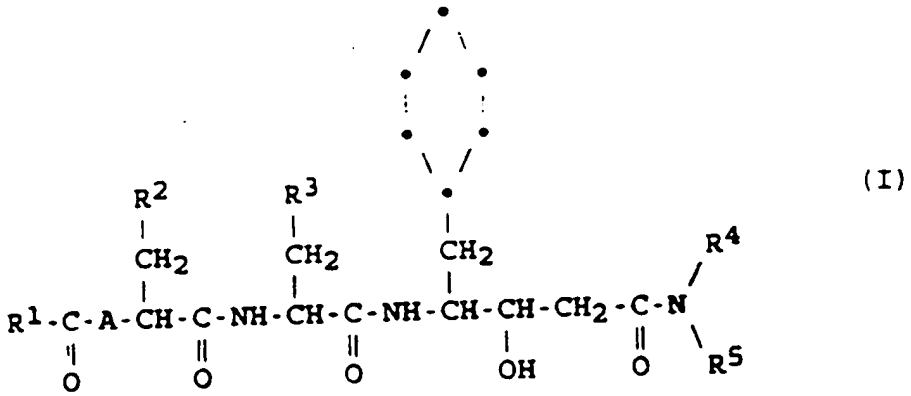


(IVb)

(dans lesquelles R^1 et R^2 sont définis comme dans la revendication 1).

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour préparer les composés de formule (I) :



(I)

dans laquelle :

R^1 représente un groupe 4-phényl-1-pipérazinyle, N-méthyl-N-benzylamino, morpholino, N-méthyl-N-cyclohexylaminométhyle, N-méthyl-N-benzylaminométhyle, N-isopropyl-N-benzylaminométhyle, benzylaminométhyle, 4-phényl-1-pipérazinylméthyle, diéthylaminométhyle, N-méthyl-N-butylaminométhyle, N-méthyl-N-phénylaminométhyle, morpholinométhyle, 3-morpholinopropyle, 4-(4-fluorophényl)-1-pipérazinylméthyle, 4-(4-chlorophényl)-1-pipérazinylméthyle, 4-(4-méthoxyphényl)-1-pipérazinylméthyle, N-méthyl-N-phénéthylaminométhyle, diisobutylaminométhyle ou 4-(4-chlorobenzhydryl-1-pipérazinylméthyle ;

R^2 représente un groupe naphtyle ;

R^3 représente un groupe thiényle, isoxazolyle, thiazolyle, imidazolyle ou isopropyle ;

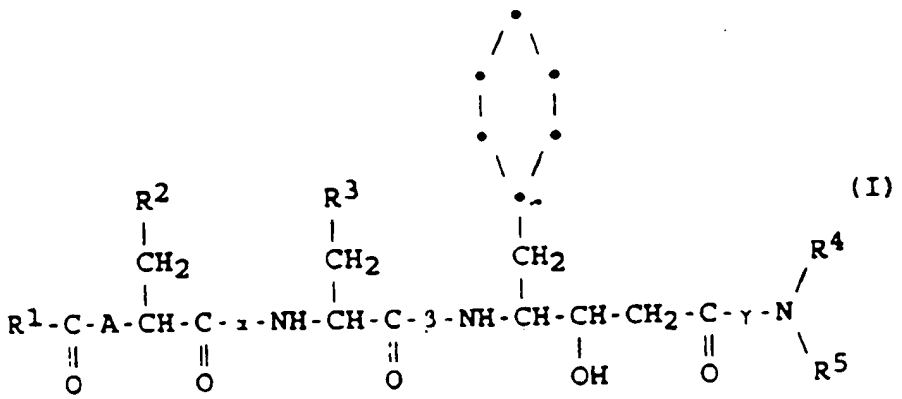
R^4 représente un groupe 2-morpholinoéthyle, propyle, butyl , isobutyle, pentyle, isopentyle, 2-méthylbutyl , hexyle, 3-(2-oxo-1-pyrrolidinyl)propyle ou 1-morpholinométhyl-2-méthylbutyle ;

R^5 r présente un atom d'hydrogène ou un groupe alkyle en C_1-C_8 ; et

A représente un groupe de formule -NH- ou $-(CH_2)_n-$, dans laquelle n représ nte 1 ou 2,

sous réserv qu lorsque R^1 r présent un gr upe benzylaminométhyle,

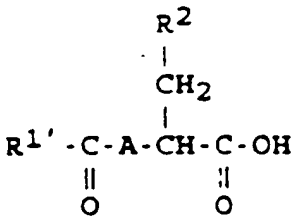
R^3 représente un groupe thiényle, isoxazolyle ou thiazolyle,
et leurs sels pharmaceutiquement acceptables, lequel procédé comprend la réaction mutuelle de deux composés, l'un ayant un groupe terminal carboxy ou un dérivé réactif de celui-ci et l'autre ayant un groupe terminal amino ou un dérivé réactif de celui-ci, dans des conditions de synthèse peptidique, lesdits deux composés correspondant aux fragments pouvant être obtenus par clivage de l'une quelconque des liaisons peptidiques marquées α, β et γ dans la formule (I) suivante dans laquelle A est un groupe -NH-, entre ce groupe et le groupe carboxy adjacent :



(I)

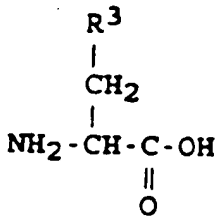
(dans laquelle R^1 à R^5 et A sont définis comme ci-dessus) ou d'un composé de formule (I) dans laquelle un ou plusieurs groupes réactifs ont été protégés, et, le cas échéant, la déprotection et/ou la salification du composé obtenu.

2. Procédé selon la revendication 1 qui comprend la réaction mutuelle des composés de formules :



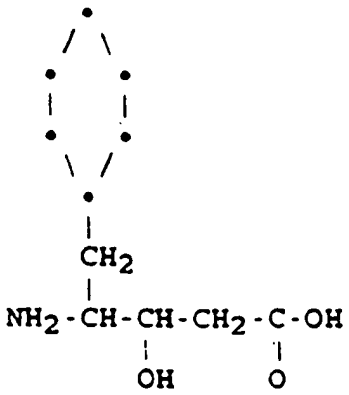
(IV)

ou d'un dérivé réactif de celui-ci,



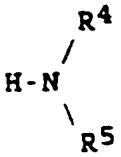
(V)

ou d'un dérivé réactif de celui-ci,



(VI)

ou d'un dérivé réactif de celui-ci, et

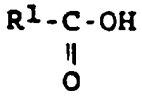


(VII)

ou d'un dérivé réactif de celui-ci (dans les formules ci-dessus, R^2 à R^5 et A sont définis comme dans la revendication 1 et $R^{1'}$ représente l'un quelconque des groupes représentés par R^1, définis comme dans la revendication 1, ou un groupe actif) et lorsque $R^{1'}$ représente ledit groupe actif, sa conversion en l'un quelconque des groupes représentés par R^1.

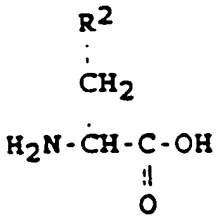
3. Procédé selon la revendication 2, dans lequel on fait réagir un composé peptidique pouvant être obtenu par réaction de certains desdits composés de formules (IV), (V), (VI) ou (VII) définis comme dans la revendication 2, ou desdits dérivés réactifs avec le reste desdits composés ou du ou desdits dérivé(s) réactif(s) ou avec un ou plusieurs composés peptidiques pouvant être obtenus par réaction du reste desdits composés ou du ou desdits dérivé(s) réactif(s) de ceux-ci, la ou les réaction(s) étant effectuée-(s) dans un ordre correspondant à l'ordre des restes dérivés desdits composés de formules (IV), (V), (VI) et (VII) dans ledit composé de formule (I).

4. Procédé selon la revendication 2 ou la revendication 3, dans lequel A représente un groupe de formule -NH- et le composé de formule (IV) est remplacé par deux composés de formules (IVa) et (IVb) :



(IVa)

et



(IVb)

(dans lesquelles R^1 et R^2 sont définis comme dans la revendication 1).

5. N-{N-[3-morpholinocarbonyl-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

6. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-DL-alanyl)cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

7. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

8. N-{N-[3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

9. N-{N-[(2R)-3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

10. N-{N-[3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl) propionyl]-3-(5-isoxazolyl)-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables,

11. N-{N-[(2R)-3-(N-benzyl-N-méthylcarbamoyl)-2-(1-naphtylméthyl)propionyl]-3-(5-isoxazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

12. N-{N-[3-morpholinocarbonyl-2-(1-naphtylméthyl)propionyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-méthylbutyl)amide et ses sels pharmaceutiquement acceptables.

13. N-{N-[(2R)-3-morpholinocarbonyl-2-(1-naphtylméthyl) propionyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-[-(S)-2-méthylbutyl] amide et ses sels pharmaceutiquement acceptables.

14. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

15. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

16. N-{N-[N-(N-méthylanilinoacétyl)-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

17. N-{N-[N-(N-méthylanilinoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

18. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]leucyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl)propyl]amide et ses sels pharmaceutiquement acceptables.

19. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-L-leucyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl)propyl]amideet ses sels pharmaceutiquement acceptables.

20. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-imidazolyl)alanyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

21. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

22. N-[N-{N-[4-(4-chlorobenzhydryl)-1-pipérazinylacétyl]-3-(1-naphtyl)alanyl}-3-(4-thiazolyl)alanyl]-cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

23. N-[N-{N-[4-(4-chlorobenzhydryl)-1-pipérazinylacétyl]-3-(1-naphtyl)-L-alanyl}-3-(4-thiazolyl)-L-alanyl]-cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

24. N-{N-[N-(N-benzyl-N-isopropylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-morpholinoéthyl)amide et ses sels pharmaceutiquement acceptables.

25. N-{N-[N-(N-b nzyl-N-isopropylaminoacétyl)-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-(2-morpholinoéthyl) amide et ses sels pharmaceutiquement acceptables.

26. N-{N-[N-(N-cyclohexyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

27. N-{N-[N-(N-benzyl-N-méthylaminoacétyl)-3-(1-naphtyl) alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-[3-(2-oxo-1-pyrrolidinyl) propyl]amide et ses sels pharmaceutiquement acceptables.

28. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(5-isoxazolyl)alanyl}cyclostatine-(2-méthylbutyl)amide et ses sels pharmaceutiquement acceptables.

29. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)-alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-(2-méthylbutyl)amide et ses sels pharmaceutiquement acceptables.

30. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-[(S)-2-méthylbutyl]amide et ses sels pharmaceutiquement acceptables.

31. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-isobutylamide et ses sels pharmaceutiquement acceptables.

32. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-propylamide et ses sels pharmaceutiquement acceptables.

33. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-butylamide et ses sels pharmaceutiquement acceptables.

34. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-pentylamide et ses sels pharmaceutiquement acceptables.

35. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-isopentylamide et ses sels pharmaceutiquement acceptables.

36. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)alanyl]-3-(4-thiazolyl)alanyl}cyclostatine-hexylamide et ses sels pharmaceutiquement acceptables.

37. N-{N-[N-morpholinoacétyl-3-(1-naphtyl)-L-alanyl]-3-(4-thiazolyl)-L-alanyl}cyclostatine-hexylamide et ses sels pharmaceutiquement acceptables.